RESEARCH ARTICLE

ANTIDOTAL EFFICACY OF TAURINE ON ACETYCHOLINESTERASE ACTIVITY AND NA+/K+-ATPASE ACTIVITY IN THE BRAIN TISSUE OF MERCURY POISONED RATS

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ABSTRACT

The effects of mercury on acetycholinesterase activity, Na+/K+-ATPase activity were studied in different tissues of rats. Experimental groups were control, mercury (5 mg/kg body wt. orally for 30 days). The acetycholinesterase activity, Na+/K+-ATPase activity were significantly decreased in mercury treated brain tissue. Our data indicate that mercury treatment inhibits significantly brain acetycholinesterase activity, Na+/K+-ATPase activity activity, demonstrating the prevalent mercury effect in vivo on central nervous systems. After mercury treatment taurine and glutathione given orally mercury (5.0 mg/kg body wt. orally for 15 days). The present result indicates acetycholinesterase activity, Na+/K+-ATPase activity was decreased in the brain tissue due to antidotal action of taurine and glutathione.

INTRODUCTION

Mercury in its various chemical forms is a ubiquitous environmental contaminant to which the general population is exposed primarily through the diet (organic mercury). The toxic potential of acute exposure to high levels of mercury compounds has been well appreciated for many years (Jagadeesan, 2004; Gerstner and Huff, 1997). Mercury is a widespread contaminant in the environment and chronic exposure to low level of Hg is quite common as a result of the contamination of food and drinking water. Mercury is highly toxic and moderate level of exposure can cause immune system alternation ranging from immune suppression to immune stimulation such as increasing susceptibility to a variety of virus, autoantibody formation and autoimmune disease (Gerstner and Haff, 1997; Koller, 1975; Sapin et al., 1977). More recently mercury has centered largely on the potential health hazards of exposure to low non-overtly toxic level of both organic and inorganic mercurial. The high affinity of mercury for protein and non-protein sulfhydryl groups is widely believed to be the biochemical basis for its harmful effects on biological system (Sankar Samipillai and Jagadeesan, 2005; Nicotera et al., 1992; Clarkson, 1997). Mercuric chloride is a neurotoxic material known for its ability to inhibit the β-esterase (acetylcholinesterase) activity in the brain tissue (Sankar Samipillai and Jagadaasan,2006; Pursottam and Kaveeshwar,

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1992). Mercury blocks the active centre of enzyme and also inhibits the synthesis of neurotransmitter. It also penetrates the blood-brain barrier, causing neurotoxicity (Huang and Narahashi, 1996). Taurine is a sulfur containing amino acid present in high concentration in mammalian cells and plasma and plays an importance role in several biological process such as development of the central nervous system, calcium modulation, membrane stabilization, reproduction, and immunity (Huxtable, 1992; Sturman, 1993; Schuller-Levis *et al*., 1990). It is also involved in cell volume hemeostatis, protein stabilization and stress response (Messina and Dawson, 2000). It was reported to be the beneficial in preventing experimental diabetic neuropathy (Obrosova *et al*., 2001) lead induced oxidative stress (Sankar Samipillai et al., 2006; 2009; 2006; 2005; Gurer *et al*., 2001) through antioxidant mechanism.

MATERIALS AND METHODS

Chemicals

Mercuric chloride (HgCl2), Taurine and all other necessary reagents of analytical grade were bought from HiMedia laboratories Ltd. Mumbai, India.

of six animals: Group-I saline (0.9% NaCl)-treated control group ; Group-II Mercuric chloride (2 mg/kg orally., for 15 days single dose)-treated group (Hg); Group-III Mercuric chloride (2 mg/kg orally single dose) + Taurine (50 mg/kg daily orally. for 15 days) treated group (Hg +taurine), Group-IV taurine (50 mg/kg daily for 10 days)-treated control group. Experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) of RMMCH, Annamalai University. The animals were sacrificed by cervical dislocation and then the whole brain tissue was isolated immediately in the cold room. The isolated whole brain tissue was used for the estimation of acetylcholinesterase(AchE) activity by the method of Metcalf (1951) and Sodium and Potassium ATPase activity was estimated by the method of Bonting (1970). Statistical significance was evaluated by using ANOVA followed by Duncan Multiple Range Test (DMRT) Duncan (1957).

RESULTS

Activity of acetylcholinesterase(AchE) in brain tissue. At sub- lethal dose of mercuric chloride treatment the rat serum shows a significant decrease in the level of AchE activity

Table 1. Changes in the level of Acetylcholinesterase (AchE) and Na$^+$ K$^+$ ATPase activity the brain tissue of rats treated with mercuric chloride follwed by taurine and glutathione

Parameters	Control	HgCl$_2$	HgCl$_2$ + Taurine	Taurine
Acetylcholinesterase (μ moles formazone formed/ mg of protein/hr.)	146.40±1.47	51.82±0.92*	138.08±0.82*	159.82±0.90
Na$^+$ K$^+$ ATPase activity (μ moles phenol liberated / min / 100 mg of protein)	108.478±0.57	125.173±0.55*	109.128±0.63*	102.602±0.85

Mean± S.D of six individual observations; Group I compared with group II; Group II compared with group III and IV;* Significance at 0.05 level

Animals

The Wister strain rats (45 days old) of the Wister strain weighing ranging from 200±5g were used in this experiment. They were divided at random into four groups (each of six rats). All the animals were fed on a standard rat feed and water *ad Libitum*. Experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) of RMMCH, Annamalai University. Wistar albino rats were divided into four groups each consisting

(51.82±0.92 μmoles of formozen formed/mg protein/hr) when compared with control rat brain. During the taurine treatment on mercury intoxicated rats (mercuric chloride followed by taurine), the decreased level of AchE activity significantly increased upto 138.08 ± 0.82 μmoles of formozen formed/mg protein/hr. During the glutathione treatment on mercury-intoxicated rats (mercuric chloride followed by glutathione), the same increasing trend was noticed. The level of AchE activity in brain was 129.12 ± 0.63 μmoles

of formozen formed/mg protein/hr. At sub-lethal dose of mercuric chloride treatment, the level of $Na^+ K^+$ ATpase activity significantly increased (125.173 ± 0.55 µ moles phenol liberated / min / mg protein). During the taurine treatment on mercury-intoxicated rats (Mercuric chloride followed by taurine), the increased level of $Na^+ K^+$ ATPase significantly decreased (109.128 ± 0.63 µ moles phenol liberated / min / mg protein). The percentage change over the mercury treatment was -12.82. During the glutathione treatment on mercury intoxicated rats (mercuric chloride followed by glutathione), the same trend was maintained (105.896 ± 0.43 µ moles phenol liberated / min / mg protein).

DISCUSSION

Heavy metal causes many physiological disorders in the organism and inhibits the enzyme activity (Ramalingam *et al*., 2002). Some of the heavy metals are known for many years to produce toxic effect on the central nervous system (Sarkar *et al*., 1998). Enzymes have the unique capacity of catalyzing extremely specific chemical reaction. They can operate under mild condition of pH and temperature. Some metal ions act as inhibitors and this inhibitory nature is taken as a technique to quantify metal inhibitors (Prameela Devi *et al*., 1999). The main toxicity of mercury and its compounds are related to the central nervous system through fast alterations in ultrastructural and biochemical machinery of neurons (Chang, 1977). These effects are due to the broad reactivity of the mercurial compounds that can cause damage to cells and tissues through diverse mechanisms, including disrupting intracellular calcium homeostatis, altering protein synthesis, disrupting membrane potential and interrupting neurotransmitters pathways (Yee and Choi, 1996).

Acetylcholineesterase is an important regulatory enzyme that controls the transmission of nerve impulses across cholinergic synapses by hydrolyzing the excitatory transmitter acetylcholine (Mitatrovic and Dettbarn, 1996). The acute toxicity of heavy metals is usually attributed to the excessive cholinergic stimulation caused by their inhibition of acetylcholinesterase. This enzyme terminates the action of the neurotransmitter acetylcholine (Ach). The resulting accumulation of Ach at the synaptic junction overstimulates the cholinergic peripheral and central receptors sites (Bajgar, 2004). In the present study, the decreased level of AchE activity was noticed in the brain tissue of rats when treated with sub-lethal dose of mercuric chloride for 30 days. This result indicates that mercuric chloride blocks the active center of the enzyme and also drastically inhibits its *de novo* synthesis. The alterations in the acetyl cholinesterase (AchE) activity in the brain of Alzheimer's patients have been reported by Balasubramaniyan (1997). Siddiqui *et al*, (1991) also reported the decreased level of AchE activity in the brain tissue of rats where treated withy monocrotophos.

The toxic effect of heavy metals on the neuroteransmitter may result from their action on subcellular process such as interference with mechanisms regulating calcium distribution in nerve terminals, and anabolic effect that may occur as a result of impairment of energy production or inhibition of enzymes involved in the synthesis and storage of transmitters. This might be due to alterations in cholinergic system in the brain tissue exposed to mercuric chloride. Inhibition of AchE appears to be the principal mode of action of toxicants (Sarkar *et al*., 2003). Mercury has been reported to cause an increase in evoked acetylcholine release followed by a sudden and complete blockade (Cooper and Manalis, 1983). Prolonged exposure to mercury results in an up-regulation of muscarinic cholinergic receptors in the hippocampus and cerebellum (Coccini *et al*., 2000). It also affects the nerve terminals. This may be due to its activity to change the intracellular concentration of Ca^{2+} by disrupting regulation of Ca^{2+} from intracellular pools and increasing the permeability of plasma membranes to $Ca2+$ (Atchison, and Hare, 1994). The inhibition of brain AchE causes the physiological and behavioural modifications that reduce the animals' survival ability (Karzmar *et al*., 1970). The inhibition of AchE disrupts the smooth transmission of the nerve impulses across the synapses causing neurosis, tremor and depression in the respiratory centers (Murthy, 1980).

Mercury mainly affects the central nervous system. The death of the animal may be due to the inhibition of AchE enzyme system by disrupting the nervous activity through the accumulation of acetylcholine at nerve endings in the central and peripheral nervous system (Margarat and Jagadeesan, 1999). Mercury has decreased the AchE leads to increased the Ach levels in various region of brain tissue of rats. The increase in Ach level has been attributed to both presynpaptic and synaptic cleft accumulation of the neurotransmitter presumably due to AchE inhibition. The role of AchE in cholinergic neurotransmission is well established. It requires detergent for solubilization and may be attached to membranes within the cell or be integral to the exterior plasma membrane (Taylor and Radic, 1994; Ferrand *et al*., 1986). AchE is a serine hydrolase, catalyzes the breakdown of the neurotransmitter acetyl choline into acetate and choline. The inhibition of AchE activity in target tissues is often taken as an indicator of heavy metal intoxication (Kwong, 2002). Brocardo *et al*., (2005) also reported that AchE activity was reduced in the cerebral cortex and hippocampus in malathion exposed rats.

The inhibitory effect on AchE activity indicates that toxicants might interfere in vital processes like energy metabolism of nerve cell (Nath and Kumar, 1999). AchE inhibitor induced cholinergic hyperacitivty initiates the accumulation of free radicals leading to lipid peroxidation which may be the initiator of AchE inhibitor induced cell injury (Yang and Dettbarn, 1996). The present investigation also confirms the brain damage which is caused by mercury. During the recovery period, the activity of AchE significantly increased in the brain tissue of rats. This result indicated that this might be due to physiological function of taurine and glutathione respectively. Taurine and glutathione not only eliminates the mercury ions from the brain tissue but also decreases the binding of Ach on the muscarinic receptors (Rajanna *et al*., 1997). And simultaneously decreased level of AchE increased to reach normal level. Margarat and Jagadeesan (1999) also observed similar result in the brain tissue of mercury-intoxicated mice when treated with penicillamine (antidote). They suggested that the increased level of AchE is mainly due to the decrease in their toxicity. An antidote not only protects the animal from the adverse effect of mercury toxicity but also proliferates the cell growth. In the present study, administration of taurine and glutathione on mercury intoxicated brain tissue, plays a vital role to detoxify the mercury toxicity. It also promotes the membrane stabilization and proliferation in the brain tissue. The present study suggests that the taurine has more efficacy than glutathione.

Heavy metals are known to alter the activities of adenosine triphosphase (ATPase), which are integral part of active transport mechanisms for cations across the cell membranes (Moore *et al*, 2003; Shaffi *et al*., 2000). ATPases are enzymes concerned with immediate release of energy and are responsible for a large part of basic metabolic and physiological activities in animals. ATPase activity can be taken as meaningful indicators of cellular activity and forms a useful toxicological tool (Rahman *et al*., 2000). The well known membrane bound transport ATPases are Na^+K^+ activated ATPase (Na^+K^+ATPase), which transport the Na^+ and K^+ across the cell membrane and play a central role in whole body osmoregulation purposes (Sancho *et al*., 2003). Na^+K^+ ATPase is a membrane enzyme responsible for the generation of the membrane potential through the active transport of sodium and potassium ions in the tissue to maintain the cellular excitability (Erecinska and Silver, 1994). Na^+K^+ ATPase is a key enzyme for maintaining the adequate cellular distributions among the enzymes particularly affected by heavy metals (Carfagna *et al*., 1996;Rajana *et al*, 1997). $Na^+ K^+$ ATPase is a well-known SH-containing enzyme in a variety of tissues (Kinne-Saffron *et al.,* 1993; Pal *et al.*, 1993; Antonio *et al.*, 2003). The Na^+/K^+ pump catalyses the hydrolysis of ATP and couples it to the transport of Na^+ and K^+ across the cell membrane thereby generating the trans membranous Na^+K^+ gradient. These pumps are essential for the regulation of cell volume, uptake of nutrients, cell growth and differentiation and are critical for the normal functioning of excitable and non-excitable tissues (Nandhini and Anuradha, 2003).

In the present study, an enhanced level of Na^+K^+ ATPase activity was noticed in the brain, liver and kidney tissues of rats when treated with

sub-lethal dose of mercuric chloride treatment for 30 days. This study represented that mercury treated tissue may be attributed to increased lipid peroxidation. Formation of lipoxygenase metabolites induces lipid peroxidation in mercury treated tissue and inactivation of Na^+K^+ activity occurs as a consequence of interaction of mercury with these enzymes. Yang *et al*, (2002) stated that elevation of Na^+K^+ ATpases activity by xenobiotics might produce adverse effects in the organism. They observed that the activity of Na^+K^+ ATpases was significantly elevated after the administration of toxicants (Hazarika *et al.*, 2003). In the present study, an elevated level of Na^+K^+ATPase could alter the signal transudation pathways of excitable and non-excitable tissues, which in turn lead to cellular dysfunction. Similar results were made by Carageorgiou *et al*. (2004) in rats treated with cadmium and Folmer *et al*. (2004) in rats when treated with heavy metals. Heavy metals mainly induced oxidative damage and increase the degradation of Na^+K^+ATPase (Thevanod and Friedmann, 1999). During the recovery period, the elevated level of Na^+K^+ ATPase activity was reduced to reach near normal in the brain, liver and kidney tissues of mercury intoxicated rats. This result indicated that the impact/influence of supplementation of taurine and glutathione could cause decrease in ROS production through reduction in autooxidation. A reduction in the production of free radicals and lipid peroxidation can beneficially prevent the Na+K+ ATPase activity. Taurine and glutathione have been reported to restore the depletion Na^+K^+ATPase activity (Sebring and Huxtable, 1985: Qi *et al.*, 1995). Similarly, Bapu *et al*. (1998) reported that the treatment of GSH in rats exposed to methyl mercury resulted in the recovery of Na^+K^+ATPase activity in rats.

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