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ORIGINAL ARTICLE

PROTECTIVE EFFECT OF TAURINE AND GLUTATHIONE AGAINST MERCURY INDUCED TOXICITY IN THE BRAIN TISSUE OF RATS

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ABSTRACT

The present study is attempted to investigate the effect of taurine and glutathione in brain tissue of mercuric chloride induced rats. The sub-lethal dose of mercuric chloride (2mg/kg body wt. of the animal) was administrated in rats orally for 30 days. In the present study, the histophathological changes were observed in brain tissue of rats. During the mercuric chloride treatment, the intoxicated brain tissue shows the irregular neuroglial cells s and vacuoles were observed. During the taurine and glutathione treatment, the restoration of histoarchitecture of brain tissue was noticed. The present study suggest that the taurine protects the brain tissue than glutathione

Keywords Mercury, Taurine, Glutathione, Histology, Brain

1.INTRODUCTION

Heavy metals are widely found in natural environment, mostly representing severe health hazard in animals (Barennan and Schiesty, 1996). The toxicological effects of pollutions are due to their high persistence and accumulation in organisms (Goyer, 1996). Although suitable concentrations of heavy metals play a vital role in metabolic pathways when their concentrations exceed the threshold limit, they act as physiological, biochemical and behavioural inhibitors in the organisms. Human activities are mainly responsible for promoting the pollution in the environment by the way of introducing unwanted toxic compounds. There is an accumulating contamination of water sources and food chain with these compounds. Four principle categories of pollutants, which jeopardize the environments, are radionucleotides, petroleum hydrocarbons, pesticides and heavy metals. Among these, heavy metals are the most dangerous ones because of their stability in the biological system (Lu, 1996). Hence, industrial pollution of the environment with metal compounds is becoming a significant problem (Foulkes, 1990).

Mercury is highly lipid soluble and enters the blood from the both lungs and mucosa. It traverses cell membrane (including the blood brain barrier and placental barrier) rapidly, partitions between plasma and red blood cells and becomes widely distributed (Engqvist *et al*., 1998). According to the agency for toxic substances and disease Registry (ATSDR) of the US department of Health and Human Services, mercury is most frequently found in the environment (ATSDR, 2001). Annual worldwide emission of mercury into the atmosphere has been estimated at 2,200 metric tones (Stopford and Goldwater, 1975). One third of these emissions are estimated to originate from natural sources (volcanic eruptions and decay of mercury containing sediments) and two third from man made sources. Twenty five percent of total worldwide emissions come from fossil fuels combustion. In the United States, 26 per cent (64.7 tons / years) of atmospheric mercury emissions come from medical waste incineration such as cremation (ATSDR, 1999). Mercury is released naturally from the earth's crust by mining, fossil-fuel combustion and other industrial activities. In the non-occupationally exposed population, however, dental amalgam is typically the major source of mercury (WHO, 1989).

Mercury (Hg) is well known as a toxic metal, but it has many applications. It is mainly used in electroplating or galvanizing because of its non-corrosive properties. It is also used a colour pigment in the preparation of paints and plastics. The Minamata disease was caused by mercury intoxication in Japan and is a notorious syndrome including severe bone deformities and chronic renal failure. The toxicity of heavy metals is extensively reviewed by many investigators (McCabe *et al*., 2005; Papp *et al*., 2005; Gatti *et al*., 2004).

Mercury is widely distributed in the environment, although in concentration lower than other heavy metals (Levinson, 1974). Mercury and its compounds are widely used in various industries (Frocasso *et al*., 2002). The indiscriminate

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discharge of mercury along with industrial effluents, sewage sludge, mine wastes, and other sources into receiving waters such rivers, lakes, and reservoirs may result into significant buld-up of the metal in aquatic environments. Mercury in human tissues comes through ingestion of food and drinking water. Human beings absorb over 90 percent of the mercury and its compounds (Rao *et al*., 2001).

Taurine (2-amino ethane sulfonic acid) is the major intracellular free β-amino acid, which is normally present in most mammalian tissues (Chesney, 1985). It is not utilized in protein synthesis, but rather is found free or in simple peptides. It plays various important physiological roles including osmoregulation, bile acid conjugation modulation of the proliferation; viability and prevention of oxidant induced injury in may tissues (Chesney, 1985; Huxtable, 1992; Redmond *et al*., 1996; Sankar Samipillai and Jagadeesan, 2004). The beneficial effects of taurine as an antioxidant in biological systems have been attributed to its ability to stabilize biomembranes (Wright *et al*., 1986; Sankar Samipillai and Jagadeesan, 2005). Scavenge reactive oxygen species (Wright *et al*., 1985) reduced the production of lipid per oxidation end products (Huxtable, 1992).

GSH is an essential tripeptide made up of the amino acid such as glutamate, cysteine, and glycine (Huxtable, 1986). The glutathione (GSH) is a cellular thiol, which is present in all mammalian tissues (Cooper, 1997). It rovides a reducing milieu for the maintenance of protein thiols and antioxidant, reduction of ribonucleotides and protection against oxidative and free radicals-mediated damage and other types of toxic injury (Deleve and Kaplowitz, 1990; Meister, 1991). The redox status of mitochondrial GSH particularly plays a vital role in cell injury since mitochondrial GSH exerts a major role in the homeostatis of $Ca2^{+}$ (Beatrice *et al*., 1984) and thiols (Kosower and Kosower, 1983) to regulate the permeability of the inner membrane. This is the most abundant endogenous non-protein thiol (Kleinman and Richie, 2000), which carries out various physiological functions such as detoxification of free radical and peroxides, regulation of cell growth and protein function and maintenance of immune function (Kleinman and Richie, 2000). From this point of view, the present study has been designed to observe the changes of histoarchitecture of brain tissues of rats when treated with sub-lethal dose of $HgCl_2$ and simultaneously withdrawal effect of $HgCl_2$ with the help of taurine and glutathione respectively.

2.MATERIALS AND METHODS

The Wister strain rats (45 days old) of the Wister strain weighing ranging from 200±5g were used in this experiments.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 six groups each consisting 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(5.0 mg/kg daily orally. for 15 days) treated group (Hg + Glutathione),Group-IV Mercuric chloride (2 mg/kg orally single dose) + Glutathione (5.0 mg/kg daily orally. for 15 days) treated group (Hg + Glutathione), Group V Taurine (50 mg/kg daily for 15 days)-treated control group and Group VI Glutathione (50 mg/kg daily for 15 days)-treated control group. The animals were sacrificed under light ether anesthesia and kidney tissues were dissected. The dissected kidney tissue used for the following estimation.

After the cervical dislocation, the experimental animals were sacrificed and selected liver was quickly isolated in cold room and fixed in buffered formaldehyde solution for 3 hrs. The tissue was washed in running tap water and processed following the standard technique (Gurr, 1959) for microtomy. The tissues were dehydrated in ascending grades of alcoholic series. The dehydrated tissue was cleaned in xylol as embedded in paraffin wax (58°C – 60°C). Serial sections were cut at 6-8 µm thickness and there were deparaffinized in xylol and after passing through descending grades of alcoholic series. The specimen sections were counter stained with aqueous haemotoxylin-Eosin stains. The stained sections were mounted on DPX for microscopical studies.

3.RESULTS

At sub-lethal dose of $HgCl_2$ intoxicated rat, *Rattus norvegicus*, brain (cerebrum) tissue shows a number of neuroglial cells. The size and shape of the neurological cells are irregular. In some area a low number of cell bodies are also evident. In the deeper layer more number of pyramidal cells are seen. But their shape and size are not uniform. Vacuoles also appear in all regions. Damaged and pyknotic nuclei are evidenced in all neuroglial cells. In some neuroglial cells, axons and dendrites are completely damaged. Damaged blood vessels are also evident (Fig. 1 and 2).

Taurine administered on $HgCl_2$ intoxicated rat brain cerebrum shows the complete restoration of its histoarchitecture. The arrangement of neuroglial is irregular. The shape and size of these cells are restored. Disappearance of pyknotic nuclei is also evidenced. Reappearance of axons and dendrites is also evident in all the neuroglial cells. Disappearance of vacuoles is also noticed in all regions. Regenerated blood vessels are noticed in all regions (Fig. 3 and 4). Glutathine treatment on $HgCl_2$ intoxicated rat could not fully retrieve the histoarchitecture of the brain cerebrum region. The size and shape of the neuroglial cells are not uniform in all regions. The irregular arrangement of neuroglial cells are also seen in all regions. Vacuoles and damaged blood vessels are also noticed. Damaged and pyknotic nuclei are seen in all regions (Fig. 5 and 6).

Taurine alone treated rat brain cerebrum shows the complete normal histoarchitecture. The size and shape of the neuroglial cells are uniformly seen in all regions. In gray region granulated stellate cells and pyramidal cells are seen in enormous number. Restoration of axons and dendrites are noticed under the higher magnification. Normal blood capillaries are also seen (Fig. 7 and 8).GSH alone treated rat cerebrum shows the incomplete histoarchitecture. The size and shape of the neuroglial cells have increased. In some area vacuoles are also seen. The number of neuroglial cells have increased in the granular layer. In between the white matter and gray cortex, the bundles of myelinated fibres are scattery distributed (Fig. 9 and 10).

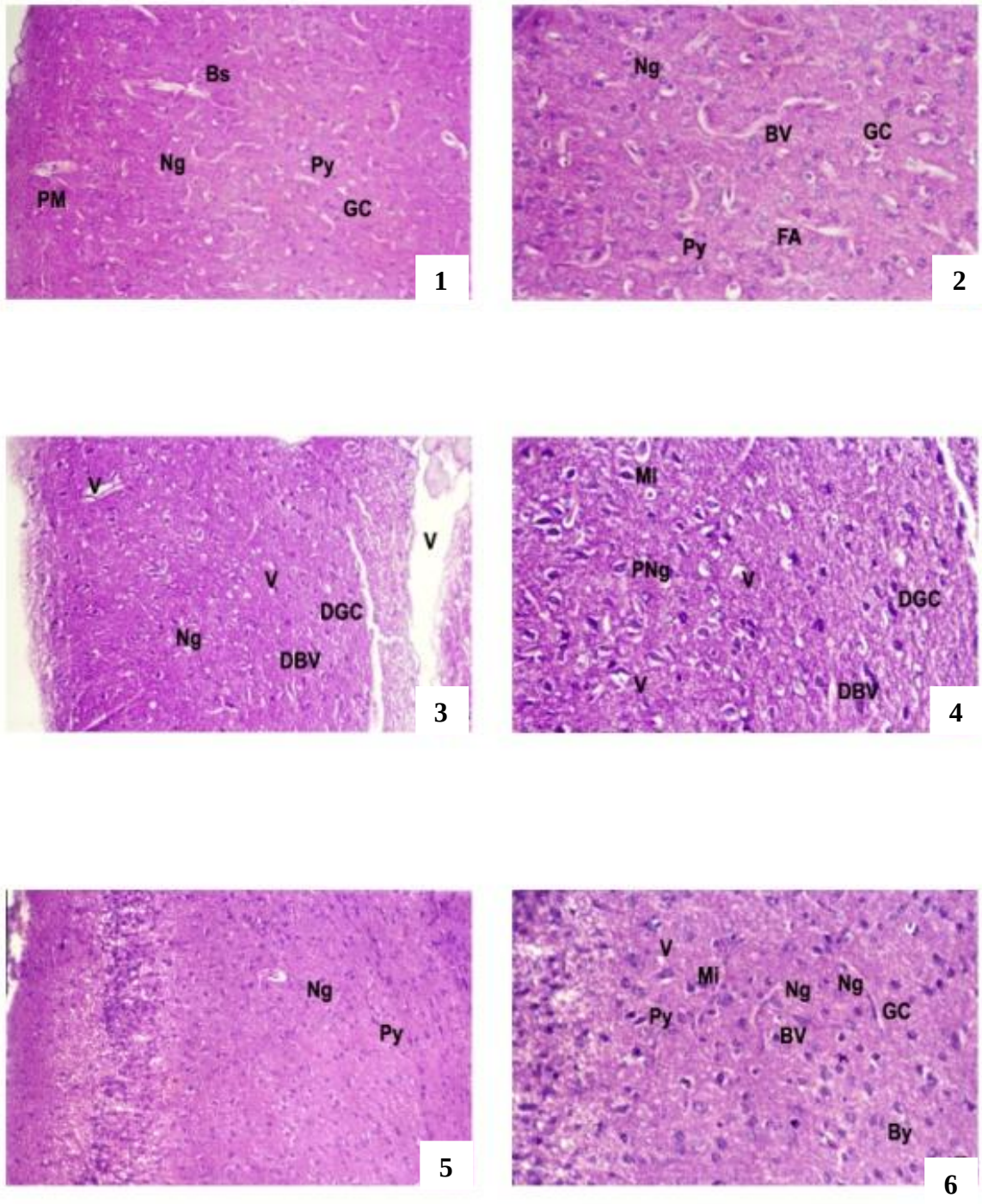

Fig. shows histology of brain tissues; 1and 2- Control brain tissue;3 and 4-Mercuric chloride treated brain tissue;5and 6-Mercuric chloride + taurine treated brain tissue

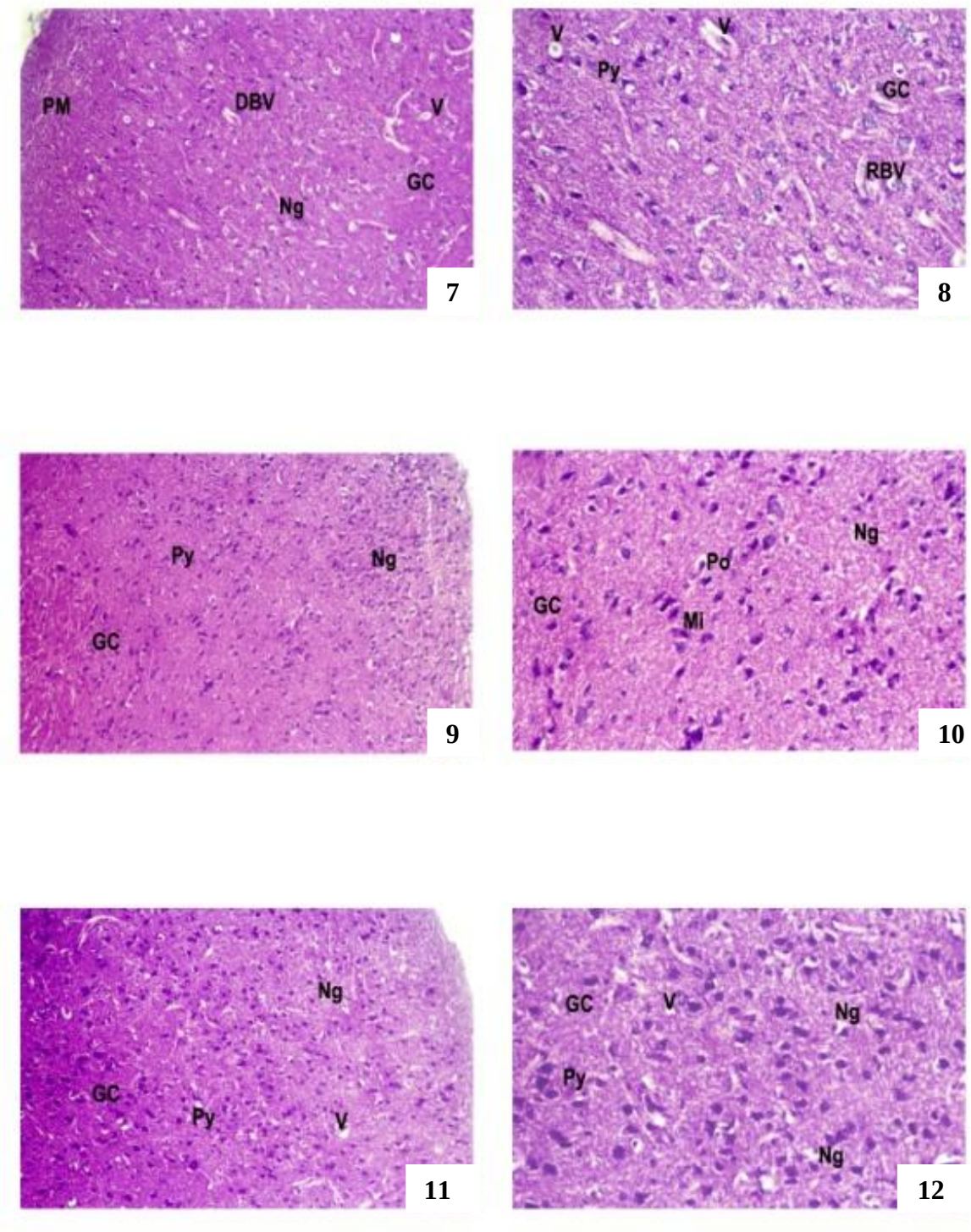

Fig. shows the histology of brain tissues; 7and 8- Mercuric chloride + glutathione treated brain tissue; 9 and 10 taurine alone brain tissue; 11 and 12Glutathione alone treated brain tissue

4.DISCUSSION

The brain is an extremely heterogeneous organ with a large number of different neuronal and non-neuronal cell types, and extensive morphological differentiation and biochemical compartmentalization within the cell (Rana *et al*., 2002). It is particularly vulnerable to oxidative damage due to the high utilization of inspired oxygen, the large amount of easily oxidizable polyunsaturated fatty acids, the abundance of redox-active transition metal ions and the relative scarcity of antioxidant defense system. Heavy metal is a neurotoxic agent in animal over 100 years but it may be involved in the pathogenesis of neurodegenerative disease such as Alzheimer's disease (AD) (Klatzo *et al*., 1965). It has also been implicated in several other neurological and non-neurological disorders. The nervous system consists of a variety of highly specialized cells including many different types of neurons and ganglia. In addition, the localization and connectivity of individual neurons influence their structure and function in the central nervous system (DeLeve and Koplowitz, 1990).

In the brain region, the heavy metal may interfere with the synthesis of specific enzymes, which is responsible for the function of brain and in turn causes neurological disorders (Cowburn *et al*., 1992). Mercury toxicity in astrocytes and neurons has implicated reactive oxygen species (ROS) contributes to mercury induced cytotoxicity (Sanfeliu *et al*., 2003). Mercury and its compounds cause damage to the central nervous system, and the accumulation of mercury in the brain leads to death (Niem *et al*., 1991). The nervous system is comprised primarily of nerve cells and neuroglial cells. The neuroglial cells not only provide the physical support but also respond to injury, regulate the ionic and chemical composition of the extra cellular fluid, precipitate in the blood –brain barrier, form the myelin insulation of nervous pathways, regulate neuronal migration during development and exchange of metabolites with neurons (Niemi *et al*., 1991). Mercury can cause demyelization, autonomic dysfunction, sensory nerve conduction delay, abnormal neuronal migration and abnormal central nervous system cell division. Chronic toxicity symptoms include parasthesis, peripheral neuropathy, cerebellar atoxia, akasthisia, spasticity, memory loss, dementia, constricted vision, dysarthria, impaired hearing, smell and taste, tremors and depression (Ozuah, 2000; Clarkson, 2002).

The present study shows the reduced number of neuroglial cells and pyramidal cells. The irregular arrangements of neurological cells are seen in all regions. The size and shape of these cells have changed. The damaged blood vessels are noticed in some area. Similar results were reported by Basu *et al*., (2000) in rat treated with calcium and nifedipine. They suggest that the heavy metal toxicities lead to an increase in the number of vacuolated spaces in the matrix which could be due to disintegration of neurological cells.The present study suggests that the loss of active movement could be possibly due to the loss of co-coordinating movements caused by the destruction of neurological cells by the toxicity of heavy metal. Mercury poisoning is more frequently involved in the central nervous system causing tremor and psycho behaviour. Severe exposure to mercury results in paralysis and death (Klassen, 1980).

During the recovery period (Mercuric chloride followed by taurine and mercuric chloride followed by glutathione), the brain tissue shows the regeneration of cells observed in all regions. These results represent the recovery from the adverse effects of mercury toxicity. The reduced number of degenerating cell bodies is seen in granular cell layer and the neuroglial cells are regenerated. These results suggest that taurine and glutathione may target the channel of energy metabolism to reduce the risk of brain damages. Similar results were reported by Margarat and Jagadeesan, (1999) in the brain tissue of mice when treated with different solvent fractions of *Tribulus terrestris* extract on mercury intoxicated animal.

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