Neurodegenerative Disorders Associated with Mercuric Chloride Toxicity in Mice and the Role of Some Antioxidant

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Abstract: Mercuric chloride toxicity experimentally induced in mice were associated with chronic neuropathology in brain including ischemic neuronal injury, spongiosis, liqufactive necrosis, perivascular and precellular edema, congestion and hyalinization of chroid plexus of lateral and fourth ventricles of the brain. These changes were observed in cerebral cortex, hypothalamus and cerebellum. The experimental animal showing clinical signs related to neuropathological changes as impared response to noise, loss of perfect movement and sleeping altitude. Co-adminstration of garlic and ginger oil together with mercuric chloride greatly inhept the above mentioned changes and result an improvement and recovery, so in area with suspected mercuric chloride pollution we advised that garlic and ginger must be a constant component of food.

Keywords: mercuric, toxicity, mice, brain

1. Introduction

Mercury is classified into three main groups[1, 2, 3]: aelemental mercury or metallic mercury (Hgo)(uncombined form), b- inorganic mercury including the metallic mercury, mercury vapor (HgO) and mercurous mercury (Hg+) or mercuric mercury (Hg++) salts (MgS, HgO and HgCl₂); c-organic mercury, also called organometallic, which results from a covalent bond between mercury and a carbon atom of an organic functional group such as a methyl, ethyl, or phenyl group[4]. According to chemical structure of mercury, various forms of mercury differ in the biological behavior, pharmacokinetics, and clinical significance [2].

There are many sources of mercury and its compounds including industrial sources: mercury emitted from fossil fuels burning as petrol and gas, fumes, battery disposals, broken mercury thermometer and coal combustion and into the air by mining cooperations, water bodies and land [5, 6]. Natural forms of mercury can be found as it is in the environment such as mercury chloride (HgCl) that is found in higher densities in rocks and volcanic activities which can give half of the HgCl₂ present in nature [7]. Photographic plates and toners contain high amount of HgCl [8]. Mercury is a common ingredient found in skin lightening soaps, creams, eye makeup cleansing products and mascara [9]. Mercuric compounds are widely used in industries and their hazards to animals have been well documented [10, 11, 12, 13, 14].

After inhalational exposure, mercury vapor readily enters the red blood cells and central nervous system [15, 16]. Both organic and inorganic mercury are readily distributed throughout the body, but tend to concentrate more in the brain and kidney and accumulate in high concentration [17, 18]. Mercury is known to bind to microsomal and mitochondrial enzymes resulting in cell injury and death [19]. Mercury is localized in lysosomes in renal tissue [18].

2. Materials and Methods

40 male and female albino mice were used for this experiment, divided into 4 groups, each contained 10 mice. Group 1: Control negative group, Group 2: administered Mercuric chloride (HgCl₂), 4mg/kg bwt (control positive group), Group 3: administered HgCl₂, 4mg/kg bwt + Garlic oil, 60mg/kg bwt and Group 4: administered HgCl₂, 4mg/kg bwt + Ginger oil, 50mg/kg bwt. All the above mentioned agents administered by oral intubation day after day for 4 weeks. Clinical signs on living animals were reported. At the end of experimental period, all mice were decapitated and brain was prepared for histopathological studies. Sections obtained from cerebrum, cerebellum and hippocampus.

3. Results

Clinical signs consists of sleeping altitude, impaired response for noise and loss of perfect fine movement were reported in mice of control positive group, but were not reported in other groups co-administered antioxidant along with Hgcl₂.

Spongiosis, focal malacia, neuronal injury of ischemic types perivascular and pericellular edema, astroglia cells reaction, congestion, thrombosis, edema and hyalinization of choroid plexus were prominent histopathological changes reported in three parts of the brain examined (cerebrum, cerebellum and hippocampus) in all cases of the control positive group. However, in group administered ginger and garlic the above mentioned changes were totally missing except for mild congestion, pericellular and perivascular edema and few cells showing ischemic neuronal injury which were only detected in the brain of few cases: see Table (1) and Figures (1-13).

Groups		Control +ve group	Garlic group	Ginger group
<u>First time point</u> (After 4th week)	Ischemic neuronal degeneration	Severe and diffuse.	Cerebrum (5-10%) Hippocampus—5% Cerebellum (10-20%)	Cerebrum (10-30%) Hippocampus5% Cerebellum Nearly healthy except single few cells.
	Perivascular and pericellular edema	Severe	Mild	Mild
	Astroglia cell reaction	Severe diffuse	Mild to moderate	Mild
	Perivascular cuff, congestion and thrombosis	Severe	Mild	Mild
	Edema of white matter	Severe	Very mild	Mild
	Malacia	Severe in grey and white matter of cerebrum.	Single focal area was observed	

 Table 1: Correlation between pathomorphological lesions in the brain of different groups under investigation

4. Discussion

In control positive group, severe histopathological changes were reported in all parts of the brain examined namely cerebral cortex, hippocampus and cerebellum. The severe diffuse changes included neuronal injury of ischemic type that involved all layer of cerebrum, hippocampus and cerebellum. Ischemic neuronal injury was associated with severe diffuse spongiosis and sometimes a focal area of liquifactive necrosis, such changes had been reported by [19, 20, 21, 22, 23].

Angiopathic changes include severe congestion, perivascular and pericellular edema and sometimes hemorrhage were prominent and severe in this group and diffusely involve all the examined layer of the brain, such changes were primary and was due to the direct effect of HgCl2. It also constitute the major factor in the pathogenesis of ischemic neuronal injury, spongiosis and liquifactive necrosis reported later on in the different parts of the brain [24, 25].

Reactive astrogliosis as well as perivascular cuff of lymphocytic type were feature of chronic neuropathy caused by toxic effect of HgCl₂. Changes in the choroid plexus which was considered as blood brain barrier [26, 27] were confined to its vasculature and consisted of congestion, edema and hyalinization of its connective tissue. Degeneration and decrease in the number of pyramidal cells which result from exposure to mercuric chloride implies the activity of hippocampus in memory formation and learning will be impaired and the role of hippocampus that involved storage and retrieval information will be also lost, these results was in agreement with [28]. Neurodegenerative disorders in cerebral cortex can affect the functional areas of the cerebral cortex which deals with skilled movement, ability to speak, appreciate pains and temperature. Musa and sadeeq [29] had reported that administration of mercury for eight days mice caused cell death in the cerebrum. The present study shows that there was loss of movement, loss of grasping and weak response to noise as a result of mercuric chloride toxicity [30, 31].

Histopathology of the brain from garlic treated group including its three investigated parts (cerebrum, hippocampus and cerebellum) was promising and showed a great improvement and tendency towards normalization. The following differences had been reported as spongiosis, focal area of necrosis was not seen in this group with prominent reduction in the number of neurons showing ischemic neuronal injury. Moreover, astrogliosis, perivascular and pericellular edema were very mild and was infrequently observed. This prominent improvement was due to antagonistic effect of garlic against HgCl₂ toxicity. These results were in agreement with [21].

Ginger with potent antioxidant effect proved to be an excellent neuroprotective product. It inhibited necrotic changes, spongiosis and ischemic neuronal injury induced by toxic effect of mercuric chloride. This inhibition was reported in the three parts of the brain under investigation including cerebrum, hippocampus and cerebellum. Moreover, a very mild perivascular edema was reported in ginger treated group. Pericellular edema and astrogliosis were insignificant and most commonly not reported. We can postulate that ginger as a neuroprotective agent was superior of garlic.

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Figure (1): Photomicrograph of cerebrum showing spongiosis of neurons and neuropils, perivascular and pericellular edema of severe degree, mild astroglia cell reaction, control +ve group, 4 weeks (H&E, x40).
 Figure (2): Photomicrograph of cerebrum showing insignificant spongiosis, garlic group, 4weeks (H&E, x40).
 Figure (3): Photomicrograph of cerebrum showing single focal area of spongiosis, ginger group, 4weeks (H&E, x40).



Figure (4): Photomicrograph of cerebrum showing diffuse ischemic neuronal injury (A), severe astroglia cell reaction, perivascular edema of severe degree, spongiosis of neurons and neuropils (B), focal area of malacia in grey matter(C), and large blood vessel with perivascular cuff (D) control +ve group, 4 weeks (H&E, x40).
 Figure (5): Photomicrograph of cerebrum showing almost complete healthy neurons, mild astrogliosis and very mild

Figure (b): I notonic fograph of cerebran showing annost comprete nearby neurons, find astroghouts and very find pericellular and perivascular edema(A), perivascular cuff(B), garlic group, 4weeks (H&E, x40).
 Figure (6): Photomicrograph of cerebral cortex showing high proportion of healthy neurons to other necrosed, astroglia cell reaction (A), perivascular edema and hypremia, perivascular cuff(B), ginger group, 4weeks (H&E, x40).



Figure (7): Photomicrograph of hippocampus showing severe spongiosis of neurons and neuropils(A), diffuse chronic neuronal degeneration of ischemic type, moderate to severe astroglia cell reaction(B), control +ve group, 4 weeks (H&E, x40).
 Figure (8): Photomicrograph of hippocampus showing very few degenerated neurons, most of neurons were healthy, garlic group, 4 weeks (H&E, x40).

Figure (9): Photomicrograph of hippocampus showing relatively small proportion of neurons suffering from ischemic neuronal injury of chronic type, ginger group, 4weeks (H&E, x40)

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Figure (10): Photomicrograph of cerebellum showing necrosis of purkenji cell layer and granular layer(A), pyknotic changes in granular layer, ischemic neuronal injury in molecular and purkenji cell layer, astrogliosis (B), Intracerebellar hemorrhage (C), control +ve group, 4weeks (H&E, x40).

Figure (11): Photomicrograph of cerebellum showing healthy molecular layer, perivascular edema, moderate astrogliosis, healthy granular layer with few single degenerated purkenji cells, garlic group,4weeks (H&E, x40).

Figure (12): Photomicrograph of cerebellum showing healthy layers, only purkenji cell layer showed single cell here and there suffering from chronic neuronal damage, ginger group, 4weeks (H&E, x40)



Figure (13): Photomicrograph of fourth ventricle showing lymphoid cell reaction (arrow) seen in its wall with increase amount of connective tissue (A), perivascular area showed some of neurons with ischemic injury (head arrow) (B) and hyalinization of choroid plexus (star) (C), control +ve group, 4weeks (H&E, x40)