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Effect of serotonin and dopamine in Pb induced behavioral deficits in rats

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Abstract: Biogenic amines namely serotonin (5-hydroxytryptamine; 5-HT) and dopamine (DA) are known to be involved in the regulation of cognitive behavior, aggression and motor control. Lead (Pb) has long been recognized as a harmful environmental pollutant all over the world. To investigate the link between lead toxicity, brain 5-HT and dopamine, effects of short term (two weeks) Pb administration were monitored on the metabolism of these Biogenic amines in rats. The rats were injected 200 mg/ml/Kg of Pb acetate daily and decapitated to monitor 5-HT metabolism after two weeks. Important findings of the study are that administration of Pb for two weeks produced a 31% reduction in the food intake and 8% reduction in the body weight. Pb significantly decreased the brain 5-HT, dopamine and HVA levels but 5-hydroxyindolacetic acid levels were not affected. Activity of rats in an open field was also reduced. Possible functional consequences of decreased brain 5-HT and dopamine concentration following Pb toxicity are discussed. It is suggested that Pb might induced decrease of brain 5-HT and dopamine might be responsible for behavioral and neurological abnormalities reported in people exposed to a Pb rich environment.

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INTRODUCTION

Serotonin (5-hydroxytryptamine; 5-HT), a neurotransmitter in the brain, is known to be involved in the regulation of memory, aggression and violent behavior[1]. As a chemical messenger, dopamine is similar to adrenaline playing a major role in addiction, mental and physical health. Increased levels of dopamine are associated with aggressive behavior [2,6]. Dopamine antagonists are the drugs that bind and are traditionally used to treat schizophrenia[3]. It is reported that low levels of dopamine are also involved in certain behavioral deficits.

Lead (Pb) has long been recognized as a harmful environmental pollutant all over the world [4,18]. It is a toxin that has the ability to impede the development and function of every organ and system in the body. The time has come to acknowledge the real dangers of lead contamination. Karachi being an industrialized city has a high rate of pollution. The lead from traffic exhausted fumes is a great danger and risk for the people living around. Lead toxicity could be the reason for the increasing number of subjects suffering from various psychological problems, like depression and tension[4,18]. Rate of suicides have also increased during the last a few years.

The present study was designed to explore the possible relationship between the lead-induced neurological problems and low concentration of serotonin and dopamine in the brain[5,6]. The findings of the investigation would be a great help in understanding the exact mechanism of lead induced neurological and behavioral impairment and to develop drugs for the treatment of Pb toxicity.

MATERIALS AND METHODS

Locally bred male Albino-Wistar rats of weights ranging from 140 to 160 gm were housed individually with free access to food and water. A total of 12 rats were equally divided into test group and control group.

200mg/ml/Kg body weight lead acetate was injected intraperitoneally to the test group for two weeks. Control animals were injected with 1ml/Kg of 0.9% saline. Food intake, growth rate and activity in an open field were monitored weekly.

All chemicals and drugs used during the study were purchased from Sigma Chemical Company (USA), BDH Chemical Pool (England). Chemicals used in HPLC analysis were of HPLC grade.

Animals were decapitated in an adjacent room to the experimental room. Blood was collected in heparinized tubes using heparinized funnels. Plasma samples were collected by centrifugation. Brains taken out immediately after decapitation had been dipped in ice-cold saline and frozen immediately in plastic storage bags and stored at low temperature (-70 0C) until analysis of neurotransmitters by HPLC-EC method was done.

Behavioral methods

A calculated amount of normal diet was given to each rat of control and test group. Intake was monitored weekly and calculated in terms of g/100g body weight. Besides percentage change in body weight was also monitored. Open field test was conducted to observe locomotor's activity.

Neurochemical methods

Frozen samples were homogenized in specific extraction medium and centrifuged to obtain supernatant. Later on the samples are analyzed for the detection of biogenic amines (5-HT and Dopamine) and their metabolites (5-hydroxyindoleacetic acid (5-HIAA), dihydroxy phenyl acetic acid (DOPAC) and homovanillic acid (HVA) by HPLC-EC).

Statistical analyses

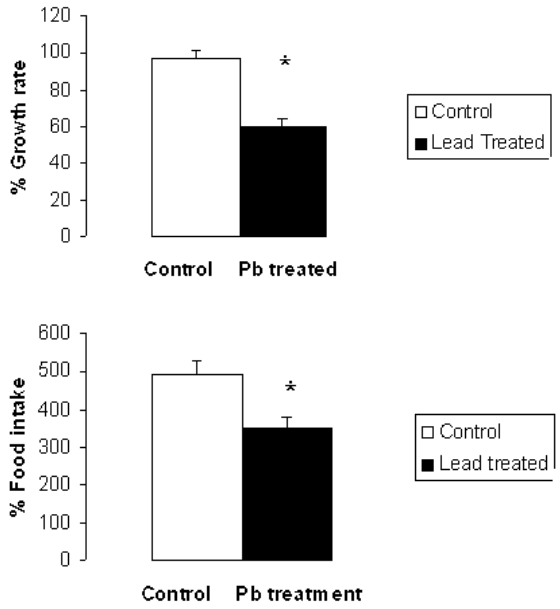
The statistical analyses were performed by Student's t-test. P values <0.05 were considered significant.

RESULTS

The results showed a significant decrease in % food intake (31%) and growth rate (8%) in lead treated animals (Figure 1a and 1b). The brain 5-HT levels were also significantly decreased in the lead treated rats (Figure 2) but the level of 5-HIAA showed no significant changes in the control and lead treated groups (Figure 3).

The level of brain dopamine and DOPAC were also significantly decreased in the lead treated group as compared to the control group (Figure 4 and 5)).

The level of brain HVA were also decreased in the lead treated group (Figure 6).



Figures 1a and 1b: Changes in food intake and growth rate of lead treated animals and controls. Data revealed a significant ($p<0.05$; 31%) decrease in food intake and ($p<0.05$; 8%) growth rate of Pb treated rats.

DISCUSSION

The increasing criminal activities, terrorism, suicides and unsocial behavior are alarming not only in Karachi but also globally. Intolerance among the people has been found to drastically increase during the last ten years[8,9].

Several studies have revealed the possible relation of Pb toxicity or increased Pb levels as a key factor behind the above-mentioned social and behavioral deficits[5,6]. Studies on serotonin have shown that low levels of this neurotransmitter are responsible for the depression and thus can lead toward such type of behavioral deficits[1,10].

It has been reported earlier that heavy metals toxicity[5,6] causes depression in humans which can be a reason for reduced food intake and hence growth rate.

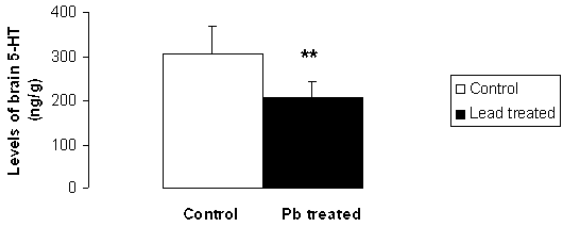


Figure 2: Difference in the brain 5-HT levels.

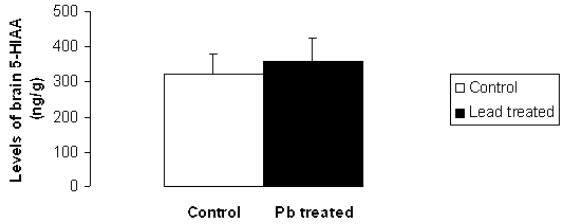


Figure 3: Concentration of brain 5-HIAA in control and lead treated animals.

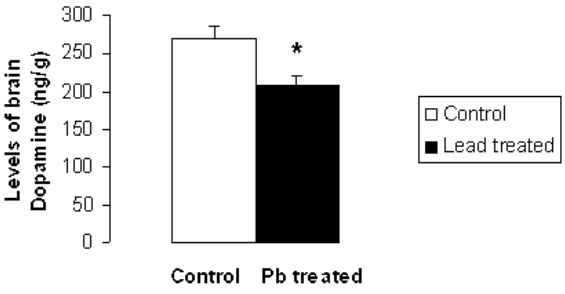


Figure 4: Levels of brain dopamine were lower ($p<0.01$) in the Pb treated group than control group.

The brain 5-HT levels were significantly decreased in the present study and it has also been reported in the previous studies[11]. It could be either

due to the increased degradation of TRP in liver by enzyme pyrrolase, leading to the decreased transportation of TRP from plasma to brain, or it could be that the activity of enzyme required for the synthesis is decreased somehow by the administration of Pb. The strong correlation between Pb exposure and decreased 5- HT might be due to the disruption of 5-HT storage pools, leading to the increased degradation of 5-HT inside the neurons by monoamines[12,13]. The levels of dopamine were also found significantly decreased in the Pb treated rats in the present study; previous studies also report this[11].

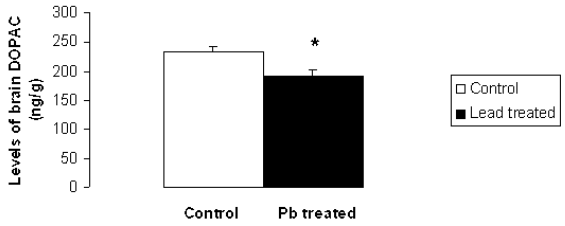


Figure 5: Brain DOPAC levels in the control and Pb treated animals.

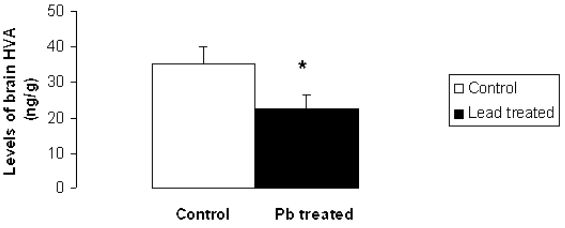


Figure 6: Brain HVA levels in the control and Pb treated rats.

The reason might be the disruption of pools of dopamine causing increased degradation by monoamines. The levels of 5-HIAA in the metabolite of 5-HT shows no significant difference while the levels of DOPAC and HVA are significantly decreased in the Pb treated animals[14] possibly due to chronic administration of Pb acetate in rats.

Open field activity was also decreased significantly in Pb treated animals. Previous studies showed that increased dopamine receptor expression in rat brain striatum increased the locomotor activity[15,16]. The reason could be the decreased levels of dopamine. Studies also reveal that decreased serotonin enhances locomotive activity[17,18], but one possible reason for decrease locomotor activity in the present study could be the depression caused by the decrease levels of Serotonin[9] due to Pb toxicity.

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