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CYTOTOXIC AND GENOTOXIC EFFECTS OF MERCURY IN HOUSE FLY *Musca domestica* (DIPTERA: MUSCIDAE)

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Abstract

Mercury, one of the most widely diffused and hazardous environmental contaminants, induces oxidative stress in organisms, which ultimately leads to genotoxicity and cytotoxicity. House fly *Musca domestica* L. was used as a model for assaying the genotoxic potential of mercury with the help of micronucleus assay, chromosomal aberration assay as end points and cytotoxicity by assaying the mitotic index and the extent of tissue damage by trypan blue dye exclusion. Late third instar larvae were exposed to different dietary concentrations of mercury (0.0001 mg/ml- 10 mg/ml) for various time intervals. A dose dependent increase in chromosomal aberrations, micronucleus frequency and mitotic index was observed. Micronucleus frequency increases with time while mitotic index decreases showing decreasing rate of cell proliferation due to an increase in cell death. Trypan blue staining gives the visual manifestation of cytotoxicity at higher concentrations of mercury (1 mg/ml- 10mg/ml). The present study suggests that the house fly model may be used to assay the genotoxicity and cytotoxicity of mercury as well as other environmental pollutants.

Key words: Mercury, Micronucleus assay, Mitotic index, Chromosomal aberration, Trypan blue.

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Abbreviations: A: Anaphase; **A.I.**: Aberration Index; **Bg**: Brain ganglia; **HiG**: Hind gut; **Gc**: Gastric caecae; **MiG**: Mid gut; **MI**: Mitotic Index; **Mt**: Malpighian tubule; **M**: Metaphase; **N.A.**: Nuclear Anomalies; **Pv**: Proventriculus; **P**: Prophase; **T**: Telophase.

INTRODUCTION

Heavy metal genotoxicity has been assayed among dipterans only in *Drosophila* (2,7,20,22,23), *Chironomus* (13,15), and *in vitro* cell line of *Aedes albopictus* C6/36 (5,6,21).

The common house fly *Musca domestica*, widely used for the studies of environmental toxicity, has, however, been used only for the analysis of the effects of heavy metals on cytotoxicity of blood cells (11), bioaccumulation, fecundity, development, survival and immuno-competence (4,19,29) and antioxidant enzyme activities (32,33).

In the present study cytotoxic and genotoxic effects of mercury have been analysed using micronucleus, chromosomal aberration assays for genotoxicity and mitotic index and trypan blue dye exclusion assay for cytotoxicity.

MATERIALS AND METHODS

Laboratory stocks of the house fly *Musca domestica* (Diptera: Muscidae) was established and maintained from the wild flies collected with the help of sweep net. Adult flies were fed on sugar and water. The milk soaked cotton

pads were provided daily for oviposition. The larvae were reared on artificial medium comprising wheat flour, wheat bran, milk powder and sufficient amount of water (1). Cultures were maintained at temperature 27 ±1ºC.

To examine whether mercury can affect development of house fly, larval mortality and the pattern of emergence was studied. The day of emergence of adult flies and the number of flies that emerged in control and different treatment groups were recorded. The larvae were treated with different concentrations of mercury divided into three categories i.e. less than LC_{50} (0.0001mg/ml, 0.001mg/ml), greater than LC_{50} (0.01mg/ml, 0.1mg/ml) and the 100 percent lethal concentrations (1mg/ml, 2mg/ml, 4mg/ml, 8mg/ml, and 10mg/ml) for varying time intervals (Tables 1-3).

For the study of genotoxicity chromosome preparations were made from brain ganglia of late third instar larvae by the standard air drying method (1) with slight modification. Slides were stained with 2% lacto-aceto orcein and cells were scored and photographed by Nikon Eclipse 80i microscope.

Total dividing cells were observed per slide and relative frequency of each type of chromosomal abnormalities and nuclear anomalies were calculated. Aberration index (A.I.) was calculated by using formula aberration index= total chromosomal aberration / total number of cells in division x 100. Micronucleus frequencies in 15000 cells in each treatment groups were scored.

Mitotic index (M.I.) was evaluated by analysing 10000 cells per treatment by using the formula mitotic index = (number of cells in division/total number of cells) x 100.

The extent of tissue damage in larvae was assayed by dye exclusion test (14). The internal tissues were explanted in PBS (phosphate buffer saline, pH 7.3), immersed in 0.2mg/ml Trypan blue in PBS and rotated for 30 min. at room temperature. The tissues were washed thoroughly twice in PBS and each group (10 larvae/ group) was immediately scored for Trypan blue staining of tissues. Degree of staining of tissues represents extent of tissue damage. Scoring for these groups of larvae was based on an average composite index per larva: no colour 0 (-), any blue 1 (+), darkly stained, 2 (+ +), large patches of darkly stained cells 3 (+ + +), or complete staining of cells in tissues, 4 (+ + + +).

RESULTS

The larval mortality increases with the increase in concentration of mercury. The larval mortality observed after different time intervals at various concentrations are represented in fig.1a. The analysis of emergence pattern reveals that there is a gradual decline in the emergence of flies from the treated larvae at different concentrations as compared to control (fig.1b). A delay of one day in emergence was observed at 0.01 and 0.1mg/ml concentrations. Thus the maximum and minimum emergences were observed at 0.0001 mg/ml and 0.1mg/ml concentrations, respectively.

A significant increase in relative frequencies of chromosome aberrations were observed in the neuroganglia chromosomes from the late third instar larvae treated with mercury (table 1). The total chromosomal aberration index shows an increase with the duration of the treatment, however, the increase does not seem to be dose dependent. The most commonly observed chromosome aberration at prophase, metaphase, anaphase and telophase were stickiness, breaks and gaps, aneuploidy, polyploidy, anaphase bridges, lagging chromosomes and telophase bridges (fig. 2). The nuclear anomalies encountered were binucleated cells, micronuclei, chromatin bridges, nuclear buds, nuclear fragmentation and endoreduplication (fig. 3). The relative frequency of nuclear anomalies decreases gradually attaining a threshold level after 0.1 mg/ml concentration.

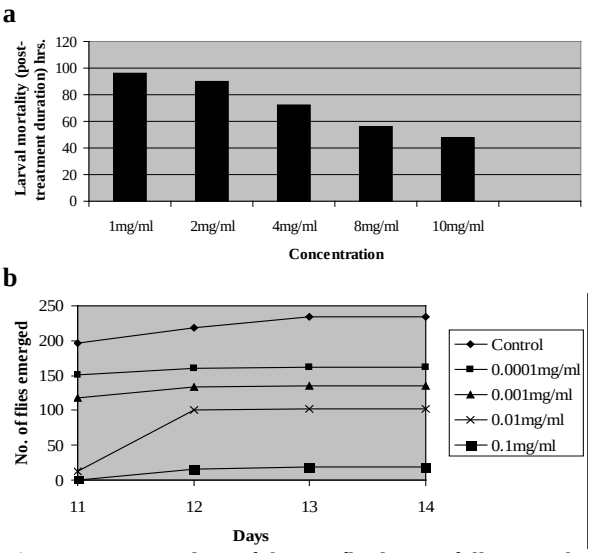

Figure1. a. Mortality of house fly larvae following the treatment with various concentrations of mercury at different time intervals. **b.** Emergence pattern of house flies following the treatment with various concentrations

The mean micronucleus frequency and mitotic index in different treatment groups and control have been summarized in table 2. A perusal of table 2 indicates that the micronucleus frequency increases in dose and time dependent manner up to 1mg/ml. Similarly, the mitotic index also shows a dose dependent increase up to 1mg/ml and a decrease with the increase in duration of treatment at all concentrations which may perhaps be due to cytotoxic effect of mercury.

The trypan blue dye exclusion assay was also performed to assess the cytotoxic effects of mercury in the present study. The extent of tissue

Table 1. Relative frequency of nuclear anomalies and chromosomal aberrations after treatment with different concentrations and for various time intervals of mercury

Concentration (mg/ml)	Duration	N.A.	Chromosomal Aberrations				
			A.I.	P	M	A	T
Control	-	0.33	6.71	-	6.15	0.56	-
0.0001	1hr.	3.38	46.84	1.53	42.20	2.12	1.99
	2hrs.	4.24	51.48	0.63	48.57	2.16	0.14
	4hrs.	4.81	53.36	1.52	49.47	1.67	1.11
0.001	1hr.	4.94	50.09	1.67	46.00	1.67	0.77
	2hrs.	5.21	53.73	1.02	48.17	3.01	1.53
	4hrs.	4.97	53.17	0.70	49.15	2.71	1.13
0.01	1hr.	4.64	48.46	0.92	44.21	3.19	1.40
	2hrs.	5.49	57.13	1.41	51.51	3.43	1.62
	4hrs.	8.38	58.18	0.67	51.61	4.43	1.31
0.1	1hr.	7.00	61.73	0.32	57.30	3.20	0.53
	2hrs.	12.49	66.48	1.49	60.59	3.12	1.41
	4hrs.	12.52	68.74	1.37	63.47	2.53	1.37
1.0	1hr.	5.87	44.01	0.50	37.17	4.94	1.28
	2hrs.	9.02	57.50	0.58	52.99	3.93	-
	4hrs.	8.71	78.35	0.54	73.94	3.39	0.48

Table 2. Mean mitotic index (%) and micronucleus frequency after treatment with different concentrations and for various time intervals of mercury

Concentration (mg/ml)	Duration	Micronucleus frequency	Mitotic index
Control	-	0.6±0.55	1.43±0.10
0.0001	1hr.	1.6±0.89	1.35±0.07
	2hrs.	2.6±1.79	1.30±0.07
	4hrs.	3.0±1.87	1.21±0.11
0.001	1hr.	2.0±0.71	1.43±0.04
	2hrs.	2.6±0.89	1.35±0.07
	4hrs.	3.2±1.48	1.41±0.18
0.01	1hr.	2.4±1.14	1.44±0.17
	2hrs.	2.0±1.22	1.36±0.15
	4hrs.	2.8±0.84	1.25±0.15
0.1	1hr.	2.6±1.14	1.66±0.16
	2hrs.	5.6±2.07	1.52±0.08
	4hrs.	5.8±1.64	1.55±0.13
1.0	1hr.	5.2±1.30	1.71±0.16
	2hrs.	6.6±0.89	1.55±0.15
	4hrs.	8.8±5.45	1.46±0.20

Table 3. Staining patterns of different tissues at various concentrations and different time intervals after treatment with mercury.

Concentration (mg/ml)	Duration	Bg	Pv	Gc	MiG	HiG	Mt
Control	-	-	-	-	+	+	-
1.0	2hrs.	+	-	+	+	+	-
	4hrs.	+	+	+	+++	+	+
	8hrs.	+	+	++	+++	++	++
	16hrs.	+	+	+	+++	+++	+
	24hrs.	++	+	+	+++	+++	+
	48hrs.	+	+	++	+++	+++	++
2.0	2hrs.	+	-	+	++	+	++
	4hrs.	+	-	+	++	++	++
	8hrs.	++	-	+	++	++	+
	16hrs.	+	+	++	++	++	+
	24hrs.	++	-	++	+++	+++	++
	48hrs.	+++	-	+++	+++	+++	+
4.0	2hrs.	+	-	+	+	+	+
	4hrs.	++	-	++	++	++	+
	8hrs.	+	-	++	++	++	+
	16hrs.	++	-	++	+++	++	++
	24hrs.	++	+	++	+++	+++	+++
	48hrs.	++	-	++	++++	++	+++
8.0	2hrs.	+	-	++	++	+	+
	4hrs.	+	-	++	+++	++	+
	8hrs.	+	-	+++	+++	++	+
	16hrs.	+	-	++	+++	++	++
	24hrs.	++	-	++	+++	++	+++
	48hrs.	++	-	++	++++	++	+++
10.0	2hrs.	++	-	++	++	+	+
	4hrs.	++	-	+	++	+	+
	8hrs.	++	-	++	+++	+	+
	16hrs.	++	-	++	+++	++	++
	24hrs.	++	-	++	+++	+++	+++
	48hrs.	+++	+	+++	++++	+++	+++

damage at the toxic concentrations at which 100% larval mortality were observed has been summarized in table 3. As compared to the controls and the larvae treated at lower doses of mercury (0.0001mg/ml- 0.1mg/ml), the tissues of the larvae treated with higher concentration (1mg/ml- 10mg/ml), reveal intense staining with trypan blue. However, the intensity of staining varies among the tissues. Thus the gut tissues i.e. gastric caecae, midgut, hindgut and microtubules reveal greater intensity as compared to other tissues. The intensity increases gradually with the time of exposure.

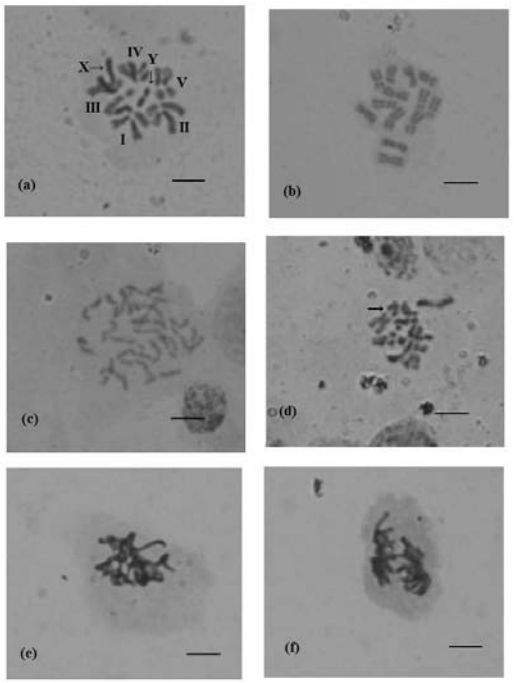

Figure 2. Neuroganglial chromosomes showing different type of aberrations (a) control (b) aneuploidy (c) polyploidy (d) gap (→) (e) stickiness (f) anaphase bridge. The bars represent 10 µ.

DISCUSSION

Mercury is one of the most widely used chemicals in the different areas, in industries, odontology, pharmacology, gold mining and agriculture, however, it is also known to be highly cytotoxic and genotoxic due to its capacity for interaction with sulfhydryl group of plasma proteins and low molecular weight, sulfhydryl rich proteins such as glutathione, and also produce free radicals which cause DNA damage (3,9,10,11,25,27,28).

The development of house flies was affected, as evidenced by a reduced emergence pattern of adult flies and increase in larval death as a consequence of cytotoxic and genotoxic effects of mercury. A delay in emergence could be attributed to the disturbance of cell division mechanisms or other cellular functions as have been suggested by Rizki et al. (2004).

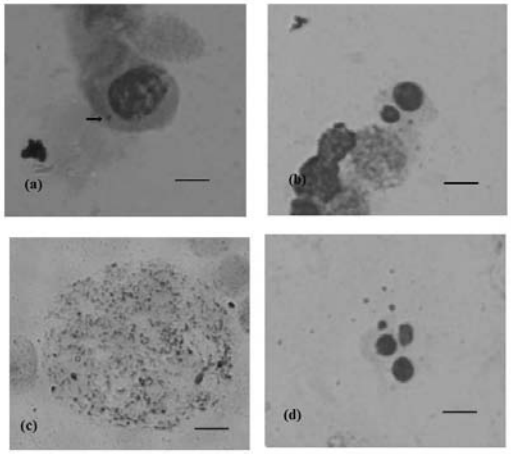

Figure 3. Nuclear anomalies induced by mercury (a) micronucleus (→) (b) binucleated cell (c) endoreduplication (d) nuclear fragmentation. The bars represent 10 µ.

The cytotoxic effects of mercury was evinced by the trypan blue dye exclusion assay and a decrease in mitotic index, which reflects cell necrosis due to a general collapse of antioxidant mechanism of the cell resulting in cell degeneration and loss of membrane integrity (25,26). Comparable results were also found in third instar larvae of *Drosophila* subjected to heat stress, argemone oil, effluents from the chrome plating industry and pesticides (12,14,16,17,18). However, an increase in mitotic index was observed with the increase in concentration of mercury which could be attributed to the ability of mercury to inhibit spindle formation (8,30,31).

The genotoxicity of mercury was confirmed by micronucleus and chromosomal aberration assays. The micronucleus frequency shows an increase with the increase in concentration and duration as has been observed in earlier studies (8,24,27,28).

In addition, various types of aneugenic and clastogenic chromosome aberrations observed in the present study also confirmed the genotoxic potential of mercury (26,28).

The present study is the first report of evaluation of heavy metal cytotoxicity and genotoxicity in house fly *Musca domestica* with the short term assays used *in vivo* and *in vitro* in

various animal groups (9). The results reveal that the housefly model can serve as an efficient system for the evaluation of genotoxic and cytotoxic potential of environmental pollutants.

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Other articles in this theme issue include references (34-49).

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