Indian J Physiol Pharmacol 1993; 37(2) : 115-120

EFFECT OF LEAD ON ANOREXIA AND BODY WEIGHT IN ALBINO RATS

R. J. AMIN, H. VENKATAKRISHNA-BHATT* AND G. M. PANCHAL

Department of Agricultural Health,
National Institute of Occupational Health,
Meghani Nagar, Ahmedabad - 380 016

(Received on June 9, 1992)

Abstract : Rats exposed to lead (lead acetate) in doses of 0.2 and 0.5 mg/ml in drinking water for a period of 90 days showed mild to moderate changes in food consumption compared to control group. Drug interactions in lead exposed rats with metoclopromide, atropine sulphate, propranolol, cyproheptadine and mepyramine maleate when administered intraperitoneally caused –30 to +30 percentage variation in food intake indicating the influence of adrenergic, serotonergic and cholinergic neurotransmitters with no change in mean body weight of lead treated rats.

Key words : lead anorexia drug interactions rats

INTRODUCTION

People are simultaneously exposed in varying degrees to lead in food, drinks and in air as well as in a number of other sources (1). The most serious effects of lead poisoning are damage to the central nervous system. At high levels of lead exposure, neural (brain) damage results as stupor, convulsion/coma and may cause irreversible damage, encephalopathy and degenerative diseases of the brain (2,3). Children are known to be more susceptible to lead poisoning for a wide variety of reasons, resulting in the impairment of cognitive and behavioural functions (4, 5).

Drugs and chemicals have widely been used in the study of food intake as they are known to cause hypo-hyper; or both effects depending on the experimental conditions (6). The investigations on the regulation of food intake were centred around two major syndromes of abnormal feeding; ventromedial hypothalamic hyperphagia (7) and lateral hypothalamic aphagia (8). Thus conceptual bilateral "satiety centre" in ventromedial hypothalamus and bilateral "feeding centre" are known (9). Here neural and chemical inputs of nutritional status of the animal are perceived besides receiving information from peripheral sources and other regions of the brain (10). Specific neurotransmitters are believed to bear links while transmitting various types of informations to the appetite centre and thus neural regulation of food intake is effected. Alfa-adrenergic receptors control feeding in the medial hypothalamic region while β-adrenergic and dopaminergic receptors in lateral hypothalamus can suppress feeding behaviour (11, 12). Serotonergic (13, 14) and cholingergic mechanism (15, 16) also influence food intake. Extrahypothalamic areas including frontal lobe, thalamus, mamillary region, periaqueductal gray matter of brain-stem, amygdala are linked with hyperphagia while aphagia and adipsia can be apparant under lesions in globus pallidus, mid brain tegmentum, substantia nigra and amygdala (15, 16). It is henceforth planned to observe influence of lead on food-intake, body weight and operant behaviour and also lead exposed rats responding to neurotransmitter mimetic drugs.

METHODS

Fifteen male charles foster albino rats of 5-6 months old, divided in 3 groups were reared in uniform climatic and animal husbandry conditions and housed separately for food intake in an 1 h/day schedule instead of 24 *h ad libitum* (17). Control group received normal tap water while test group I and II received lead acetate 0.2 and 0.5 mg/ml *per se* in drinking water. Food offered was only bengal gram for a period of 90

*Corresponding Author

days. Drugs metoclopromide (specific peripheral dopaminergic blocker), cyproheptadine (serotonergic blocker) mepyramine maleate (specific histamine$_1$ blocker) atropine sulfate (muscarinic cholinergic blocker) and propranolol (specific β-adrenergic receptor blocker) were administered intraperitoneally one hour prior to the experiments in the doses of 10 mg, 1 mg, 1 mg, 2 mg and 10 mg/kg body weight in the control and test groups. The emphasis had been to expose consistantly to lead at low doeses over twelve weeks and to evaluate daily food intake in rats which received tap water, lead and drugs alone (control) and drugs and lead (test groups I and II).

Statistical analysis : The mean food intake (MFI) as g/100 g body weight in control, lead and drug treated groups were determined. The mean average (comparative) was calculated in all the groups.

RESULTS

Rats exposed in drinking water containing 0.2 and 0.5 mg/ml lead acetate showed mild to moderate changes when compared to control (Fig. 1, Table I) in respect of mean food intake on different days. The results present no significant change in the anorectic activity.

Anorectic activity and the drug interactions : Metoclopramide (10 mg/kg), cyproheptadine (1 mg/kg), atropine sulphate (2 mg/kg), propranolol (10 mg/kg) and mepyramine melate (1 mg/kg) failed to produce any significant change in test group I and II when compared to control group (Fig. 2, Table II).

TABLE I : Chronic effect of lead 0.2 and 0.5 mg/ml in drinking water in 23 hr fasted rats. Mean food intake (Mean ± SD)

Group	*Mean food intake ng/100 g b wt ±S.D.*						
	Days						
	1	15	30	45	60	75	90
Control	9.34±1.82	8.11±2.19	9.04±1.09	9.41±3.01	9.52±1.18	10.56±1.79	7.80±1.13
Lead 0.2 mg/ml	8.32±3.9	5.95±2.32	8.14±2.92	7.53±2.99	8.75±1.49	8.07±1.98	6.54±1.06
Lead 0.5 mg/ml	9.23±1.89	8.06±1.94	9.84±2.36	7.54±1.30	8.30±2.11	8.50±1.40	6.84±1.14

P = <0.05 (The successive mean values were compared by paired 't' test)

TABLE II : Effect of drugs and its interaction in chronically orally lead (0.2 and 0.5 mg/ml in drinking water) treated rats on mean food intake (M.F.I.) (Mean ± S.D.).

Name of drugs and its ip	*Groups (M.E.I.) ing/100 g b wt/Rat/hr*		
	Control	*Lead 0.2 mg/ml (Test group I)*	*Lead 0.5 mg/ml (Test group II)*
Metoclopramide 10 mg/kg, ip	6.77±1.8	8.34±2.76	6.43±2.76
Cyproheptadine 1 mg/kg, ip	6.48±1.08	5.17±2.39	6.57±2.83
Mepyramine 1 mg/kg, ip	7.75±1.09	8.20±1.28	8.36±1.51
Atropine sulfate 2 mg/kg, ip	8.64±0.64	7.28±1.80	7.01±3.06
Propranolol 10 mg/kg, ip	8.32±1.22	8.90±1.63	8.74±1.85

NS : Successive mean values were compared by paired 't' test. Comparison done between the control and test groups.

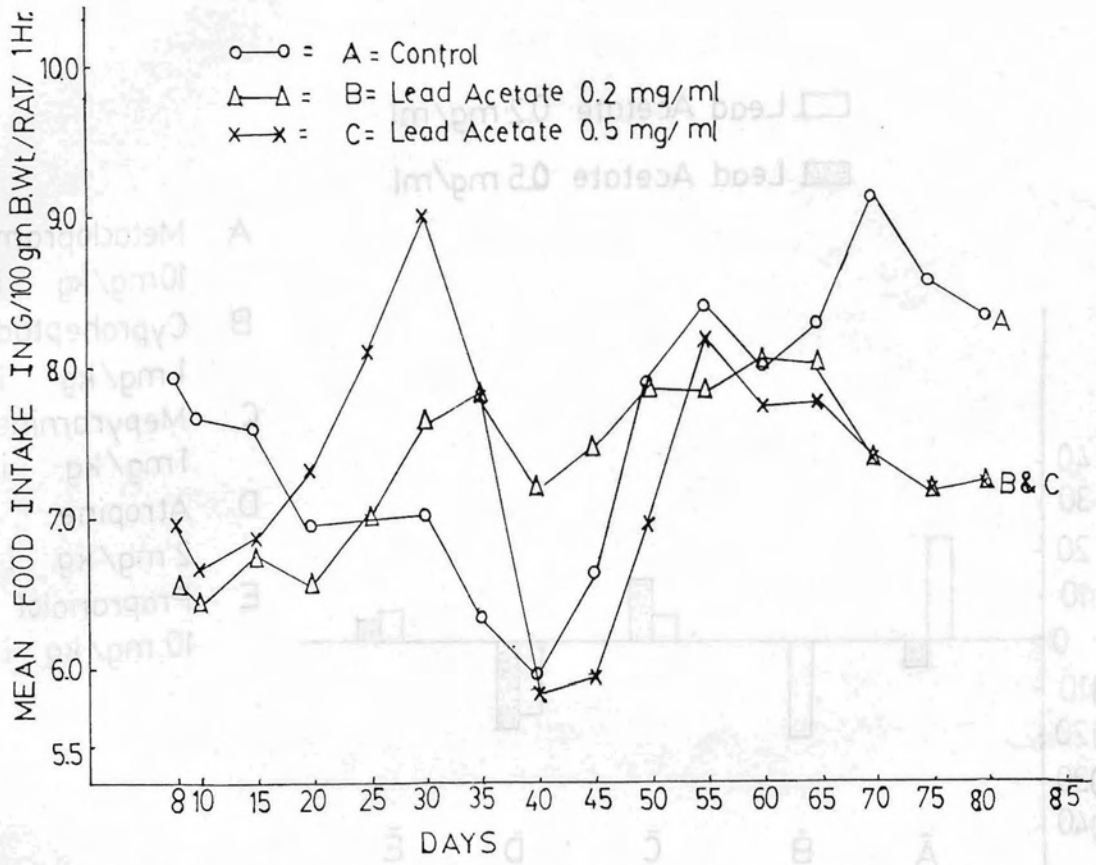

Fig. 1 : **Effect of chronic oral lead acetate** on food intake in rats. Mean food intake on different day in two doses (0.2 and 0.5 mg/ml) in g/100 g body weight/hour in rat. Each point represents the mean of five observations.

Lead and body weight : Rats treated with 0.2 and 0.5 mg/ml lead acetate moderate changes in moving average of body weight in group I and II when compared to control group (Table III).

TABLE III : Shows body wt. of control and test group I and II on different days (Mean ± S.D.).

Group	*Mean food intake wt ± S.D. and days*						
	1	15	30	45	60	75	90
Control	107.00 ± 34.97	127.00 ± 39.73	125.00 ± 38.58	136.00 ± 39.77	144.50 ± 37.74	150.00 ± 32.78	155.55 ± 32.44
Lead 0.2 mg/ml	196.50 ± 91.59	203.75 ± 79.98	196.25 ± 81.92	193.75 ± 74.84	197.85 ± 76.91	195.00 ± 62.24	206.66 ± 62.18
Lead 0.5 mg/ml	167.00 ± 48.48	180.00 ± 44.17	181.00 ± 51.52	188.00 ± 79.78	187.50 ± 50.40	191.50 ± 44.22	197.00 ± 43.28

$P < 0.05$ (The successive mean values were compared by 't' test) Chronic effect of lead 0.2 and 0.5 mg/ml in drinking water in 23 hr fasted rats (Mean body wt ± S.D.).

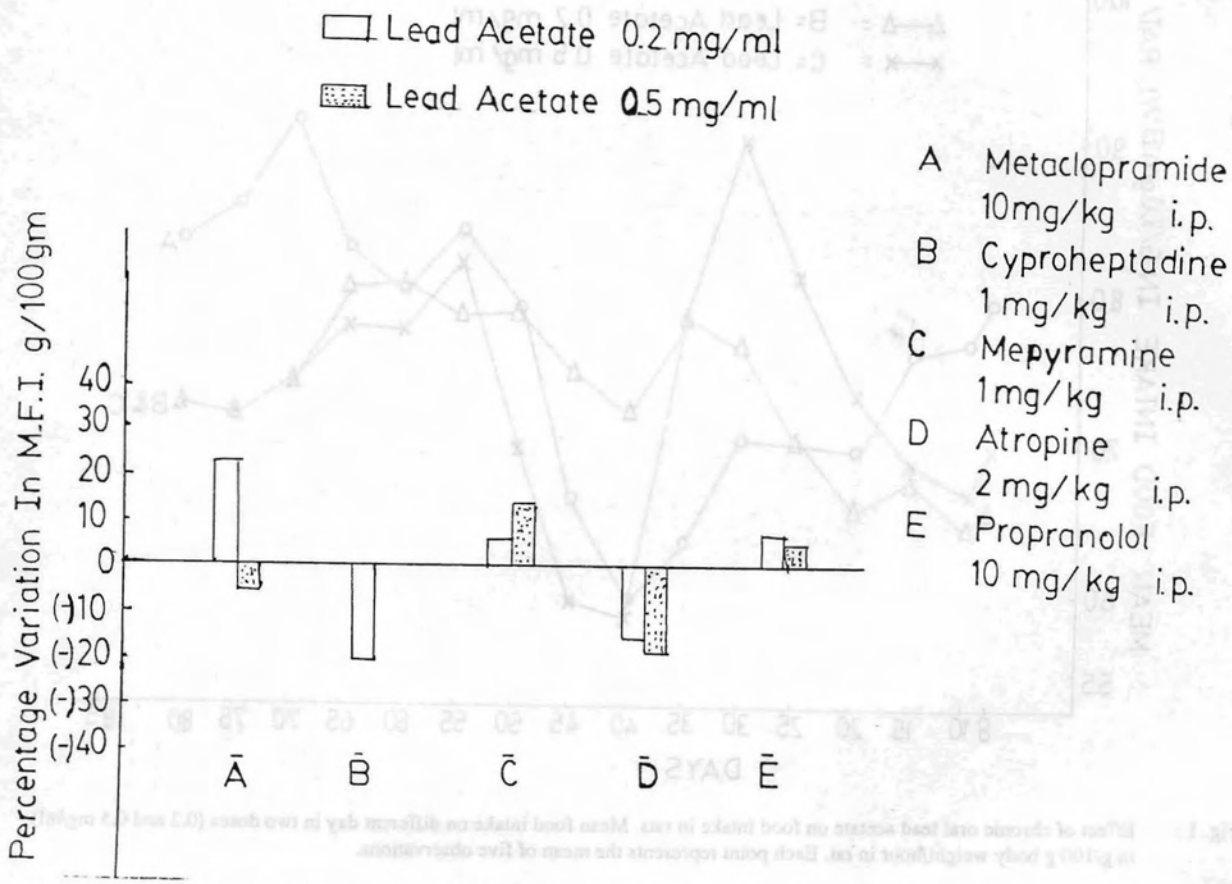

Fig. 2 : Percentage variation in mean food intake in g/100 g/rat and the influence of chronic oral lead acetate (0.2 and 0.5 mg/ml) and its interaction with drugs metaoclopramide, cyproheptadine, mepyramine, atropine sulphate and propranolol in 10, 1, 1, 2 and 10 mg/kg i.p. in rat. Each point represents the mean of five observations.

DISCUSSION

A number of pertinent questions related to the neurobehavioural activity of lead are still largely unanswered. Among these, the following are relevants: (1) Are subclinical effects of low level exposure to lead, real or spurious? (2) what is the spectrum of such effects? (3) How about the their reversibility after cessation of exposure? (4) Is there a thresh hold for lead induced neurobehavioural deficit? (5). What are the mechanism underlying neurobehavioural deficit associated with chronic low-level lead exposure ?

Higher centres for food intake, other than the ventromedial and lateral hypothalamus also play an important role in the control of food intake and body weight gain mechanism. These extrahypothalamic sites include frontal lobe, thalamus, mamillary region, amygdala which are linked with hyperphagia while globus pallidus, midbrain tegmentum, substantia nigra,

lower brain stem and basal ganglia are concerned with aphagia and adipsia (19). Defects in functions of the nervous system have serious consequences under acute and severe chronic exposure to lead (6). It is apparent that both brain and peripheral neural tissues are affected depending upon morphological and behavioural effects (2, 5, 6, 20). The behavioural evidence suggest that behaviour disrupted by hippocampal lesions such as avoidance, learning radial arm maze and Hebb-William's maze are also disrupted by exposure to lead (21-23). On the neurotransmitter side, low doses of lead indicated alterations in several aspects of catecholaminergic function in the rat brain (24); but in our study propranolol a specific β-adrenergic blocker and metoclopromide a specific peripheral dopaminergic blocker failed to produce significant anorectic effect of lead acetate in the test groups meant either it could be due to insufficient doses of catecholamine blockers or may be effect on central system. Cyproheptadine, a specific serotonergic blocker also failed to induce any effect in lead groups indicating non-involvement of serotonin. Cholinergic system is also influenced by lead exposure (25) but in this study atropine sulphate (26) a specific muscainic cholinergic blocker also failed to affect the cholinergic centres. The mechanism or reason may be either due to inadequate dose of atropine or lead acetate. However, the role of cholinergic mechanism in feeding regulations remains to be unclear. Further, mepyramine maelate, a specific histamine blocker (H_1) had no anorexia in group I and II indicating the involvement of either some non-specific or catecholaminergic mechanism. Neurobiological evidence relating limbic system lesion and behavioural alterations have been useful as a guideline in evaluating the result of neurotoxicity studies involving lead (27) with reasons to explain why lead causes anorexia and reduction in body weight. To elucidate the mechanism of action, how neurotransmitters affect the food intake and body weight in the lead acetate treated rat deserves further work in this regard. The present studies indicate that chronic exposure to lead at the dose levels used sets in variations in food intake which is either compensated or like a basement when the cumulative effects help to develop specific behavioural deviations and may set decline in normal behaviour of food intake etc in rats.

ACKNOWLEDGEMENTS

The authors acknowledge with thanks support and encouragement by the Director, National Institute of Occupational Health, Ahmedabad during the period of this study.

REFERENCES

1. Harrison RH, Laxen DPH. Chapter 7. Human exposure to lead and its effects in 'Lead Pollution - Causes and Control Published by Chapman and Hall, New York, NY 10017, 1984; 133-158.
2. Judith MR, Judith LR. Assessing behavioural and cognitive effects of diet in pediatric populations in "Nutrition and the Brain" Vol. 6. Physological and Behavioural effects of Food Constituents (Ed. RJ Wurtman and JJ Wurtman), Raven Press: New York 1983, 101-162.
3. Shailesh-Kumar MV, Desiraju T. EEG Spectral power reduction and learning disability in rats exposed to lead through postnatal developing age. *Indian J Physiol Pharmacol* 1992 ; 36 (1) 15-20.
4. Chisolm JJ. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. *J Pediat* 1968 ; 73 : 1-5.
5. Needlemen HL. Lead at low dose and behaviour of children. *Acta Pschiat Scand* 1983 ; 67 (Suppl. 303) : 26-37.
6. Blundell JE. Biogrammer of feeding : harmacological manipulations and their interpretations. In : Progress in Theory and Psychopharmacology. (Ed. S.J. Cooper), Academic Press, London Pp. 233-276.
7. Brobeck JR, Tepperman J, Long CNH. Experimental hypothalamic hyperphagia in the albino rats. *Yale J Biol Med* 1943 ; 15 : 831-853.
8. Anand BK, JR. Hypochalamic control of food intake in rats and cats. *Yale J Biol Med* 1951 ; 24 : 123-140.
9. Stellar E. The physiology of motivation *Psychol Rev* 1954 ; 61 : 5-22.
10. Grossmany SP. Role of the hypothalamus in the regulation of food and water intake. *Psychol Rev* 1975 ; 82 : 200-224.
11. Leibowitz SF. Reciprocal hunger regulating circuits involving alpha and Beta adrenergic receptor located respectively in the ventromedial and lateral hypothalamus. *Proc Nat Acad Sci (USA)* 1970 ; 67 : 1063-1070.
12. Leibowitz SF. Brain catecholaminergic mechanisms for control of hunger In "Hunger : Basic Mechanisms and Clinical Imlications" (Ed. D. Novin, W. Wyrwicka and G. Bray) Raven Press, New York 1936, 1-18.
13. Breisch ST, Zemlan FP, Hoebel BG. Hyperphagia and obesity following serotonin depletion by intraventricular p-Chlorophenylalanine. *Science* 1976 ; 192 : 382-385.

14. Saller CF, Stricker EM. Hyperphagia and increased growth in rats after intraventricular injection of 5, 7-dihydroxytryptamine. *Science* 192 ; 385-387.

15. Grossman SP. Direct adrenergic and cholinergic stimulation of hypothalamic mechanisms. *Am J Physiol* 1962 ; 202 : 872-882.

17. Ghosh MN. Fundamentals of Exprimental Pharmacology. *Scientific Book Agency, Calcutta (India)* 1984 ; 153-158.

18. Quenouille NIH. Rapid statistical calculations 2nd Edn. Charles Griffin & Co. Ltd. London 1972 ; 36-37.

19. Sullivan AC, Cheng L. Appetite regulation and its modulation by drugs. "Nutrition and Drug Interactions. (Ed. JN Hathock, J Coon) Academic Press Inc. New York (Nutr. Foundation-Monograph Series) 1978 ; 21-82.

20. Zoltan AV. Mechanisms of neurotoxicity and their relationship to behavioural changes. *Toxiocology* 1988 ; 48 : 219-225.

21. Christopher W, Ian K. Lead Neurotoxicity : A review of the biochemcial neurochemcial and drug induced behavioural evidence. *Prog Neurobiol* 1984 ; 22 : 59-87.

22. Shailesh-Kumar NV, Desiraju T. Regional alterations of brain biogenic amines and GABA/glutamate levels in rats following lead exposure during neonatal development. *Arch Toxicology* 1990 ; 64 : 305-314.

23. Schellenberger MK. Effects of early lead exposure on neurotransmitter systems in the rat brain. A review with commentory. *Neurotoxicology* 1974 ; 5 : 177.

24. Winder C. The interaction between lead and anticholinergic function. *Biochem Pharmacol* 1982 ; 23 : 3717-3721.

25. Wenk GL, Otton DS. Lesion analysis. In Z. Annu (Ed) neurobehavioural Toxicology. *The John Hopkins Press, Baltimore* 1986 ; Pp. 268.

26. Shih TM, Hanin. Effects of chronic lead exposure on levels of acetylcholine and choline and acetylcholine turnover rate in rat brain areas *in vivo*. *Psychopharmacology* 1978 ; 58 : 263-269.

27. Rossuouw J, Offermeiter J, Van-Rooyen JM. Apparent central neurotransmitter receptor changes induced by low-level lead exposure during different development phases in the rat. *Toxicol Appl Pharmacol* 1987 ; 91 : 132-139.