

CHAPTER - 2

2. INTRODUCTION

Cadmium in various forms is so widely distributed in our environment that it has been called the dissipated element (Petering et al., 1979). Its wide distribution is a result of modern industrialization and of practices required by urbanization and modern agricultural economics and of change in life style (Friberg et al., 1975). Human exposure to cadmium is a result of its presence in the work place of a number of industries, and its occurrence in soils, food, water, cigarette smoke, and pollution due to burning of coal, erosion of rubber tyres, and use of cadmium, as an anti-corrosive coating for steel product.

In India, it has been observed that more than 50% of the soil sample from Punjab and Haryana are sandy with low organic matter, low pH, and are deficient in zinc; these conditions are favourable to promote cadmium uptake by the plants (Chandra, 1980). Fertilizers like superphosphates, rock phosphate, diammonium phosphate, used in Punjab (India) contained cadmium (Singh, 1976). Sea waters from Bhavnagar, Gonga and Mandapam used for preparation of salts contained cadmium more than the recommended permissible limit (Chandra, 1980). A survey of heavy metal content in water and sediments of Sursagar lake of Baroda (India) has shown that the cadmium contents were higher than the maximum allowable

limits (Agrawal et al., 1978). Therefore, a majority of people exposed to cadmium receive it via food, water, smoking, and inhalation of fumes from the industry.

Tissue distribution of cadmium has been studied in various parts of the world by a number of investigators. In a comprehensive report by Schroeder and Balassa (1961), evidence was presented that cadmium deposition was cumulative with kidney and liver having the highest levels. Schroeder (1960) and Schroeder and Balassa (1961) showed that renal cadmium among the Japanese was 6030 ppm ash with a range of 1390-19500 ppm ($SE \pm 800$), Delhi-Lucknow Indian 2120 ± 310 , Bangkok Thai 4910 ± 1470 and Nigerian Negro 1700 ± 150 . Liver levels of cadmium though about one-tenth the respective renal levels, showed a similar pattern.

Experimental evidence obtained from controlled laboratory condition suggests that cadmium may function in or may be an etiological factor for various pathological processes including testicular tumour, renal dysfunction, growth inhibition, chronic diseases of old age, atherosclerosis, cancer and hypertension (Flick et al., 1971). Though cadmium causes a wide range of pathological effects, its role in hypertension has attracted much attention in recent years.

The issue of an etiological role of cadmium in hypertension has been considered for the last two decades and

this property constitutes one of the baffling enigmas in cardiovascular research. Debate continues as to whether cadmium causes chronic hypertension either clinically or experimentally. The clinical data offer both support (Schroeder, 1965; Mackenzie and Kay, 1973; Glauser et al., 1976) and refutation (Beever et al., 1976; Ostergaard, 1977; Dally et al., 1978) of a positive association. Experimental data on rats are equally equivocal; when ion is fed both positive (Schroeder and Vinton, 1962; Schroeder, 1964; Schroeder and Buckman, 1967; Kanisawa and Schroeder, 1969a; Perry and Erlanger, 1971a, 1974a, 1975, 1978, 1980, 1981, 1982; Perry et al., 1977, 1979, 1980; Petering et al., 1979; Walker and Moses, 1979; Fadloun and Leach, 1980) and negative (Lener and Bibr, 1971; Doyle et al., 1975; Loeser and Lorke, 1977; Eakin et al., 1980). hypertensive effects have been reported under comparable experimental conditions. When cadmium was repeatedly injected intraperitoneally both success (Schroeder et al., 1966, 1970; Schroeder and Buckman, 1967; Thind et al., 1970a, 1973; Fadloun and Leach, 1981) and failure (Porter et al., 1974) to induce a chronic hypertensive state have resulted. Unquestionably, the injection of cadmium solutions intraperitoneally, intravenously or intraarterially in rats elicits a prompt acute pressor response. Negative findings have not been reported.

Moreover, the mechanism of cadmium-induced hypertension is a subject of considerable debate and controversy till date. Several possible mechanisms have been suggested,

- (a) increased sodium retention (Perry et al., 1971; Foulke et al., 1974; Doyle et al., 1975; Perry and Erlanger, 1980, 1981),
- (b) direct vasoconstriction (Perry et al., 1967; Perry and Erlanger, 1975),
- (c) hyperreninemia (Perry and Erlanger, 1973),
- (d) involvement of sympathetic system (Revis, 1977; Revis and Zinsmeister, 1981; Fadloun and Leach, 1981a),
- (e) involvement of prostaglandins (Caprino et al., 1982),
- (f) reduction of urinary kallikrein activity (Boscolo et al., 1981),
- (g) through influx of calcium ion (Niwa and Suzuki, 1982).

There are also considerable discrepancies regarding the effect of cadmium on vascular and nonvascular tissue. Toda (1973a) has shown that cadmium ion decreased the responses to K^+ , noradrenaline (NA), barium, and angiotensin (ANG) in isolated rabbit aorta. However, the effect of NA was more resistant to Cd^{++} than that of K^+ (Toda, 1973a). These results are different from those reported by Thind et al. (1970b) who found that Cd^{++} is a potent inhibitor of NA

than K^+ . On the contrary Niwa and Suzuki (1982) showed that cadmium produced contraction in low concentration and relaxation in high concentration in the rat aorta. In intestinal smooth muscle of guinea-pig ileum, cadmium is shown to produce inhibitory effect on responses to various agonists (Triggle et al., 1975). On the contrary, Asai et al. (1982) showed that cadmium produced bell-shaped dose response curve in longitudinal muscle of guinea pig with contraction in low doses and inhibition in high doses. In cadmium treated hypertensive rabbits, there was decrease in responsiveness to ANG, not to NA (Thind et al., 1970a).

The impact of cadmium on the environment is undoubtedly increasing (Lancet, 1976) and because hypertension is a common disease associated with higher morbidity and mortality, it is important that the relationship if it exists, be clearly delineated. The necessity, with a critical appraisal of the discrepant clinical and experimental findings, has been the subject of an editorial by a leading medical journal (Lancet, 1976).

From the foregoing discussion, it is evident that there are quite a few controversial opinions regarding the role as well as the mechanism of cadmium induced hypertension in experimental animals. More in vitro pharmacological studies are also required to be carried out which might help in

understanding the mechanism of cadmium-induced hypertension. Recently Templeton and Cherrian (1983) on their review on cadmium and hypertension clearly emphasised the need for further studies on these lines for their possible relevance to human health. Therefore, an investigation on the effects of cadmium on experimental animals is of considerable interest for the evaluation of its impact on the health of general population and especially its contribution to health problem.

Thus, the present work on 'Some pharmacological investigations of cadmium' is aimed at studying

- (a) mechanism of acute blood pressure response to intravenous and intraperitoneal administration of cadmium in rats,
- (b) mechanism of chronic hypertension induced by cadmium in rats,
- (c) in vitro sensitivity of isolated vascular and non-vascular tissues of rat to various agonists in the presence of cadmium;
- (d) in vitro sensitivity of isolated vascular and non-vascular tissues to various agonists of cadmium treated hypertensive rats,
- (e) histopathological evaluation of some organs after chronic treatment with cadmium in rats.

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