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Effect of Manganese on Some Aspects of Carbohydrate Metabolism in Rats

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Numerous biochemical and toxicological studies have indicated that chronic exposure to manganese leads to neurological abnormalities (COTZIAS 1968, TOLONEN 1972, CHANDRA et al. 1974, SETH et al. 1977). Increasing use of manganese compounds as antiknocks in gasoline and diesel fuel (HYSELL et al. 1974) has aroused a great concern over the toxicological potential of this metal and stressed the need for understanding the mechanism of its poisoning. Reports of alterations in the levels of biogenic amines have helped in understanding the basis of neurological disorders. However, little is known about the mechanism by which manganese exposure leads to hypoglycemia in workers (RUBENSTEIN et al. 1962, HASSANEIN et al. 1966).

This study deals with the influence of manganese exposure on metabolism of glucose, the chief fuel of the brain, and some enzymes involved in its oxidation. These studies will provide an assessment of the extent to which manganese affects the various processes controlling carbohydrate metabolism.

MATERIALS AND METHODS

Twenty-four adult female albino rats (140 $\pm$ 10g) of Industrial Toxicology Research Centre animal breeding colony maintained under standard animal husbandry conditions were divided into two equal groups. One group of animals were given manganese (10 mg/kg body weight, i.p. in 0.1 mL normal saline, single injection) and the animals of the other group received the vehicle in the identical manner to serve as controls. The treated and control animals were further subdivided equally into two groups. Blood samples from six treated and six control animals were collected from tail vein in oxalated tubes at 0, 1, 3, 5, 8, 24, 36, and 48 h for glucose determination. The animals were not given any food during this time and were sacrificed by decapitation after the last blood collection. The remaining six treated and six control animals were used for the collection of blood at 72 h after the manganese treatment. Immediately after killing, livers were removed and divided into two portions. One portion was used for the isolation, purification (GOOD et al. 1933), and estimation of glycogen (MONTGOMERY 1957). The other portion was homogenized in 0.25M sucrose with the help of a Potter-Elvehjem type C homogenizer fitted with a teflon pestle to yield 10% (w/v) homogenate which was used for estimation of enzyme activity. Activity of phospho-

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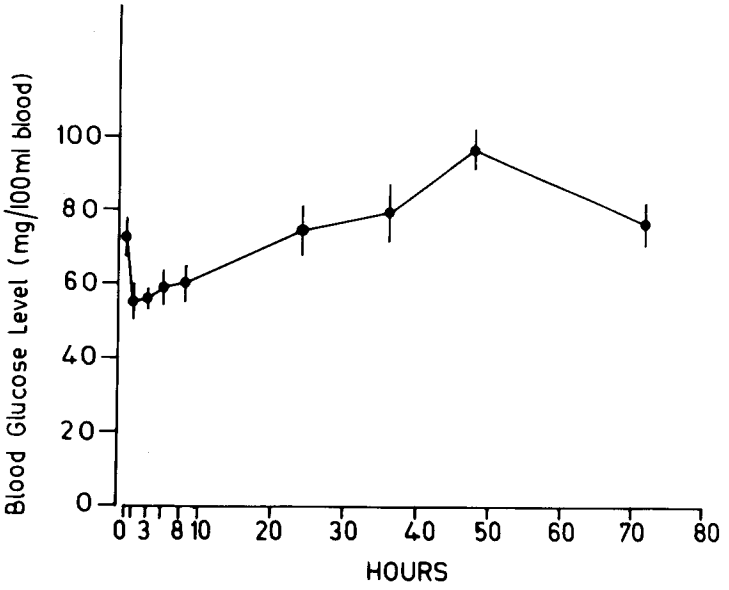

Fig. 1. Effect of Manganese on Blood Glucose Levels at Different Time Intervals

glucoisomerase (Glucose-1-phosphate ketolisomerase, E.C. 5.3.1.9) and fructose diphosphate aldolase (Fructose-1,6-diphosphate-D-glyceraldehyde 3-phosphate lyase, E.C. 4.1.2.13) were estimated by the methods of GLOCK et al. (1956) and SIBLEY & LEHNINGER (1949), respectively. Activity of glucose-6-phosphatase (D-glucose-6-phosphate phosphohydrolase, E.C. 3.1.3.11), and fructose-1,6-diphosphatase (D-fructose-1,6-diphophohydrolase, E.C. 3.1.3.11) were estimated as described by SWANSON (1955) and POGELL & MCGILVERY (1952), respectively. Liver protein was estimated by the method of LOWRY et al. (1951) using bovine serum albumin as a standard.

RESULTS AND DISCUSSON

As evident from Figure 1, the blood glucose levels following manganese exposure decreased significantly in the early periods and then showed a trend to increase. At 48 h, the blood glucose level was 36% higher in treated rats as compared to controls. These observations suggest that manganese exposure leads to hyperglycemia after an early hypoglycemia.

Data presented in Table 1 show the effect of manganese on certain enzymes of glycolysis and gluconeogenesis. Manganese significantly elevated the levels of two glycolytic enzymes, aldolase, and

TABLE 1. Effect of manganese on certain enzymes of carbohydrate metabolism and glycogen content in rat liver

Parameter	Specific activity Control	Treated	Percent Change
Phosphoglycoisomerase (nmoles fructose-6 phosphate formed/min/mg protein)	444 ± 29	729 ± 29*	64 (+)
Aldolase (nmoles fructose 1,6-diphosphate hydrolysed/min/mg protein)	52 ± 8	80 ± 8**	55 (+)
Fructose 1,6-diphosphatase (nmoles Pi liberated/min/mg protein)	42 ± 7	42 ± 6	-
Glucose-6-phosphatase (nmoles Pi liberated/min/mg protein)	62 ± 4	59 ± 5	-
Glycogen (mg/gm fresh tissue)	4.4 ± 0.3	1.8 ± 0.5	58 (-)

Each value is the mean ± S.E. of six animals.

*$P<0.001$; **$P<0.05$.

phosphoglucoisomerase without effecting the activity of two key gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-diphosphatase. Liver glycogen content was reduced by 58% at 48 h of exposure.

Our results indicate that in the manganese induced increase in blood glucose levels glucogenesis has no significant role. The increase in glucose levels may perhaps be due to the increased breakdown of hepatic glycogen and activation of glycolytic enzymes. Alterations in the level of insulin, cyclic AMP, and bivalent cations can be responsible for these manganese induced changes. Carbohydrate metabolism is influenced by the alterations in level of insulin, release of which is activated by cyclic AMP. A reduced cyclic AMP levels have been observed in chronic manganese poisoning. High concentration of manganese are also reported to inhibit the activity adenyl cyclase (PRASAD 1975). The decreased level of cyclic AMP will lead to a reduced insulin release which may presumably account for the observed hyperglycemic effects. Histopathological studies have, however, shown that manganese damages the acinar cells of the pancreas without effecting the islets of langerhans (CHANDRA & MUSTAFA 1970).

In addition, data provided by WIMHURST & MANCHESTER (1972) suggest that several glycolytic and gluconeogenic enzymes which require magnesium as a cofactor are also activated by small amounts of manganese (1 mM), though higher concentrations are inhibitory. The exact reason for this was not offered in their study. They also observed that another bivalent cation calcium was inhibitory to the same enzymes. An increase in serum calcium content has been observed both in patients suffering from manganese poisoning and experimental animals without any symptoms of hypercalcemia (CHANDRA et al. 1973). Therefore, increase in manganese or calcium contents due to chronic exposure to manganese may lead to impairment of carbohydrate metabolism.

HUSSANEIN et al. (1966) have concluded from their clinical studies that the hypoglycemic phase along with the other physiological factors may exert a profound influence on the physiological functions of the central nervous system. Thus, a feedback mechanism may be operating whereby initial disturbances causes hypoglycemia which in turn increases the neurological disorders. Our studies suggest significant alterations in the carbohydrate metabolism as judged by glucose levels and activity of some enzymes of carbohydrate metabolism. Although the exact mechanism is not understood, alterations of insulin levels appears to be responsible for such effects of manganese.

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