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Influence of Partial Hepatectomy on the Metabolic Disposition of Nickel in Rats

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Liver plays an important role in the metabolic disposition of various endogenous and exogenous chemicals and also has a capacity to detoxify large number of potentially toxic metals (Conney 1967; Thomas et al. 1976; Sammett et al. 1979; Maines and Kappas 1977; Siegers et al. 1986). Any insult to this organ may, therefore, lead to various disorders. Several recent studies on the metabolism and distribution of nickel have generated a great deal of interest in nickel induced toxicity (Sunderman Jr. et al. 1976; Smith and Hackley 1968; Clary 1975; Okarson and Tjolve 1979; Peers et al. 1983; Carvalho and Ziemer 1982; Whanger 1973). However, little information is available on the effect of liver injury on the toxicity and distribution of nickel. The aim of the present study was to evaluate the effect of liver injury on the distribution of nickel in tissues, its binding to subcellular fractions and excretion in urine and feces. Experimental studies were conducted using partially hepatectomized rat liver as a model.

MATERIALS AND METHODS

The experimental animals of Industrial Toxicology Research Centre colony were six weeks old female albino rats weighing approximately 120 g. They were housed in an air-conditioned room and had free access to pellet diet (Hindustan Lever Ltd. India) and water. Partial hepatectomy (70%) and sham operations were performed under light ether anaesthesia under aseptic conditions (Higgins and Anderson 1931). Immediately after operation each rat received a single subcutaneous injection of 63-nickel (50 u mole nickel/kg containing 200 u Ci 63-$NiCl_2$, specific activity 6.3 m Ci/mg, New England Nuclear, USA). This dose was selected since it was non-toxic even in partially hepatectomized rats as it did not produce any biochemical alterations. Both sham and partially hepatectomized rats (six animals each) were placed individually in the glass metabolic cages for urinary and fecal excretion of 63-nickel for a period of 16 hrs and were sacrificed by decapitation. Liver, kidney, lung, spleen and heart were immediately removed, washed and cleaned free of extraneous material. For the measurement of radioactivity in these organs, known weight of the tissues were subjected to acid digestion and finally evaporated to dryness. The residues were decolourised with ten drops of hydrogen peroxide (30% aqueous solution) and were again evaporated to dryness. Samples were finally dissolved in 0.5 ml water and 15 ml of scintillation fluid. Radioactive 63-nickel was counted on a LKB Rack Beta 1215 liquid scintillation spectrometer and quenching corrections were made in each sample. Measurements of 63-nickel radioactivity in urine and feces were performed as reported elsewhere (Sunderman Jr. et al. 1976)

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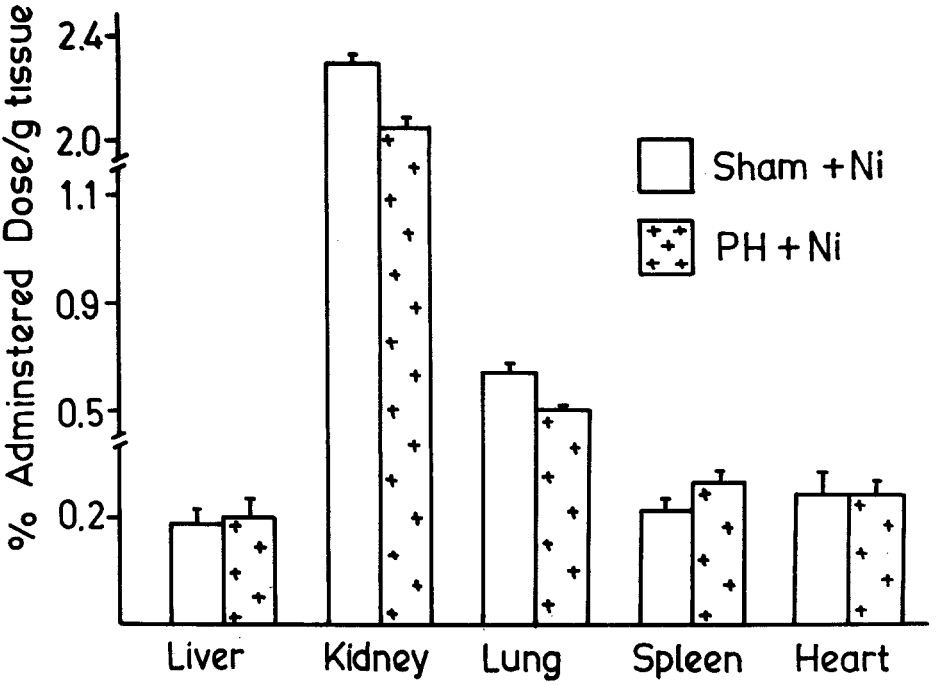

Figure. 1. Distribution of 63-Nickel in various organs of sham operated (Sham) and partially hepatectomized (PH) rat 16 hrs after the administration of nickel. Each bar represents the average value ± SEM (n = 6) per group.

For the intracellular localization studies, portions of liver, kidney and lungs of each group were pooled and homogenized in ice-cold 0.25 M sucrose solution (10% w/v) and cellular fractions were separated by differential centrifugation (Dwivedi et al. 1982). Radioactive nickel in each sample was counted by taking a known aliquot of each fraction after processing as described for tissues.

RESULTS AND DISCUSSION

The relative distribution of 63-nickel in organs of sham and partially hepatectomized rats are shown in Figure 1. Our results of nickel treatment of sham operated rats confirm the previous observation that kidney is the major site of accumulation of nickel followed by lung, heart, spleen and liver. Administration of nickel to partially hepatectomized rats also revealed a similar pattern. The results further demonstrate that partial hepatectomy did not produce any significant change in the per cent accumulation of nickel/g tissue compared to sham operated rats. The urinary and fecal excretion of 63-nickel upto 16 hrs after the administration of nickel averaged to about 50% and 1% respectively of the administered dose in partially hepatectomized rats and was not significantly different than sham operated rats.

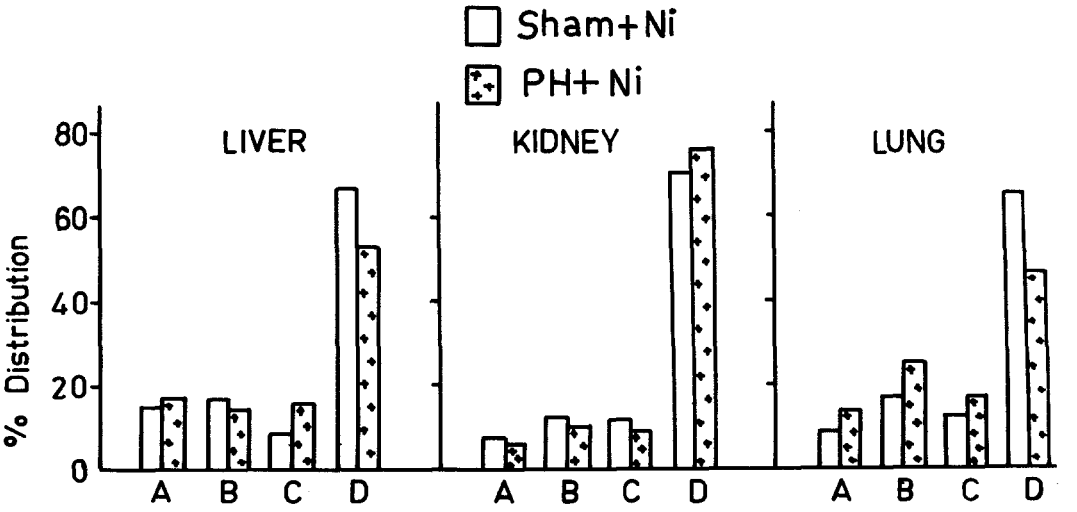

Figure 2. Distribution of 63-Nickel in A - nuclear, B - mitochondrial, C - microsomal and D - cytosolic fractions of liver, kidney and lung of nickel treated sham operated (Sham) and partially hepatectomized (PH) rats.

Data on the subcellular fractions of liver, kidney and lung of sham and partially hepatectomized rats are shown in Figure 2. In all the three organs more than 60% of 63-nickel was present in the soluble fraction (cytosol) and is consistent with the previous report (Whanger 1973). Partial hepatectomy led to a significant decrease in the accumulation of nickel in cytosolic fraction of lung with corresponding increase of 1.5 fold in rest of the fractions. Partial hepatectomy also increased the accumulation of nickel (2 fold) in hepatic microsomal fraction.

Studies on the toxicokinetics of nickel in rats have revealed that it is mainly accumulated in kidney, rapidly cleared from blood and excreted mainly in urine (Sunderman Jr. et al. 1976; Clary 1975; Carvalho and Ziemer 1982). The results of the present study demonstrate that in partially hepatectomized rats a large fraction of nickel was accumulated in kidney as well and was mainly excreted through urine. The low accumulation of nickel in liver of sham and hepatectomized rats and similar urinary excretion data suggests that liver is not the only target organ for the metabolic disposition of nickel and that urinary excretion is rather the favoured route of its excretion (Sunderman Jr. et al. 1976; Carvalho and Ziemer 1982; Marzouk and Sunderman Jr. 1985).

Several binding proteins have been implicated in the cellular storage and transport of nickel **in vivo** (Okarson and Tjolve 1979; Peers et al. 1983; Behari et al. 1984). The high accumulation of nickel in kidney of normal rats have been explained in terms of its binding to low molecular weight metallothionein like proteins (Peers et al. 1983). It has also been speculated that nickel readily binds to hepatic proteins which are ultimately transported to various sites and specifically retained in the kidney

(Peers et al. 1983; Behari et al. 1984). In partially hepatectomized rats where 70% of the liver is removed the extent of nickel binding to liver proteins would be greatly diminished and, therefore, less nickel bound proteins would be transported to kidneys and other extrahepatic tissues as compared to sham operated rats. The unaltered distribution of nickel in the tissues of sham and hepatectomized rats thus demonstrates that liver proteins are not apparently responsible for the transport of nickel to various extrahepatic tissues entirely.

Binding of nickel to nuclear, mitochondrial, microsomal and cytosolic fractions of liver, kidney and lung after the administration of nickel salts to rats has been reported earlier (Peers et al. 1983; Whanger 1973). These investigations show differences in the nickel binding capability in the insoluble subcellular components of lung and liver; the preferential incorporation of nickel in the insoluble fractions of lung becomes obvious in the present study. These results could be of significance in the understanding of nickel metabolism.

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