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FIBRO PROLIFERATION IN THE CCL4 TREATED HYPO AND HYPERTHYROIDIC RATS

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ABSTRACT

Carbon tetrachloride promoted fibroproliferation in the liver. A decrease in collagen content was recorded in the liver of hyperthyroidic and carbon tetrachloride treated rats, however, an increase was recorded in hypothyroidic and carbon tetrachloride treated rats.

Key words: Collagen, hydroxyproline, carbon tetrachloride, L-thyroxine, thyroid, liver.

INTRODUCTION

Fibroproliferation is characterized by excessive connective tissue accumulation and slow but continuous tissue contraction that cause progressive deterioration in the normal structure and function of an affected organ. Now a days, research in diverse fields has increasingly highlighted the potential role of mechanobiology in the molecular mechanisms of fibroproliferation. Hepatic fibrosis occurs in advanced liver disease, where normal liver tissue is replaced with collagen rich extracellular matrix.If it is left untreated, results in cirrhosis. Fatty changes may occur with tetracycline.

MATERIALS AND METHODS

For the proposed investigations, the rats were divided into 6 groups, each containing 10 rats. The body weight of rats was recorded each day and the food intake was regularly monitored. A record of the change in body weight was maintained. Experimental protocol followed in this study is described in table 1.

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Table 1: Experimental protocol employed in present study

Group	Treatment	Dose administered/kg body weight	Vehicle/route	Duration of treatment
A	Control	0.2 ml/kg body weight	Olive oil only	Each alternate day for 30 days
B	Carbon tetrachloride	0.2 ml/kg body weight of 2% carbon tetrachloride	Olive oil/intramuscular	Each alternate day for 30 days
C	6-N-propyl-2-thiouracil (PTU)	6-N-propyl-2-thiouracil (2.5 µg/100 gm body weight)	Distilled water/intramuscular	Twice a week for 30 days
D	L-thyroxine	L-thyroxine (25-30 µg/100 gm body weight)	Distilled water/intramuscular	On each 4th day for 3 weeks
E	PTU + carbon tetrachloride	After 2.5 µg PTU/100 gm body weight for 30 days (twice a week). Intramuscular 0.2 ml/kg body weight of 2% carbon tetrachloride.	Distilled water/olive oil/intramuscular	30 days + 30 days
F	L-thyroxine + carbon tetrachloride	After L-thyroxine (25 - 30 µg/100 gm body weight) for 3 weeks. Intramuscular 0.2 ml/kg body weight of 2% carbon tetrachloride	Distilled water/olive oil/intramuscular	3 weeks + 30 days

After required days of treatment, the rats were starved for 24 hours and then sacrificed by decapitation in the morning hours.

For studying fibro proliferation, collagen from the liver was extracted by the method suggested by Fitch et al. (1955) using trichloroacetic acid.

Hydroxyproline, a reliable marker of collagen metabolism was estimated in urine samples using the colorimetric method. Absorbance was recorded at 550 nm.

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OBSERVATIONS

Fibrosis

(a) Collagen

Present observations on liver collagen show that CCl_4 causes massive fibrosis. However, liver collagen decline in hyper as well as in hypothyroidic rats (Table 2).

(b) Hydroxyproline

Urinary hydroxyproline is treated as a reliable marker of liver fibrosis (collagenesis). These results show that CCl_4 causes significant increase in collagenesis of liver. However, a significant decline in collagenesis was observed in hyperthyroidic and carbon tetrachloride treated rats. Whereas no affect of carbon tetrachloride on collagen in hypothyroidic rats was recorded (Table 3).

Table 2: Effect of hypo and hyperthyroidic conditions on collagen in the liver of rats treated with carbontetrachloridetreated rats.

Group	**Treatment**	**Collagen (gm/gm dry liver)**
A	Control	0.062± 0.072
B	Carbon tetrachloride	0.068± 0.052
C	Hypothyroidic	0.140± 0.0136
D	Hypothyroidic + carbon tetrachloride	0.120± 0.0110
E	Hyperthyroidic	0.050± 0.0085
F	Hyperthyroidic + carbon tetrachloride	0.040± 0.0075

Results are expressed as mean ± SE (n=5)

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Table 3: Effect of hypo and hyperthyroidic conditions on urinary hydroxyproline incarbon tetrachloride treated rats

Group	Treatment	Hydroxyproline (mg/l)
A	Control	6.320 ± 0.0179
B	Carbon-tetrachloride	5.060± 0.0550
C	Hypothyroidic	4.900± 0.0
D	Hypothyroidic + carbon tetrachloride	5.200± 0.0
E	Hyperthyroidic	3.000± 0.0
F	Hyperthyroidic + carbon tetrachloride	3.200± 0.0

Results are expressed as mean ± SE (n=5)

DISCUSSION

Liver fibrosis is one of the most important pathological manifestations of liver injury caused by several xenobiotics and disease states. The cirrhotic liver fibrosis is characterized by regenerating nodules that modify hepatic architecture and function. It has been reported in hepatitis, human cirrhosis (Chen and Leevy, 1975), alcoholism (Shaba et al., 1973), heavy metal poisoning (Rana and Prakash, 1986) and experimental liver injury by carbon tetrachloride (Chaudhary and Rana, 2013). Present resultshow that carbon tetrachloride treatment causes an increase in fibrogenesis. Several studies have postulated that excessive synthesis and deposition of collagen is responsible for progression of liver injury. The pathophysiology of hepatic fibrosis has been studied extensively by Popper and coworkers (1961). They proposed that fibrogenesis occurs due to condensation of reticulum in the manufacture of new collagen either by fibroblasts or other related cells. Furthermore, several workers have demonstrated that collagen is produced by other cell types also, including the hepatic parenchymal cells. Electron microscopical studies have suggested that ductular cells which proliferate in cirrhotic conditions stimulate fibrogenesis and produce collagen.

Thyroidic manipulations as shown by present result affected collagen synthesis and metabolism. A decrease in collagen content was noticed in the liver of carbon tetrachloride treated hyperthyroidic rats, however, an increase was recorded in hypothyroidic and carbon tetrachloride treated rats It has been shown that collagen metabolism is under the control of an enzyme known as collagenase. Hyperthyroidism may activate the enzyme collagenase. Contrarily hypothyroidic conditions may not accelerate or stimulate the enzyme activity leading to excessive deposition of collagen in the hepatic tissue.

Another way of studying connective tissue disorder in liver injury is to determine the hydroxyproline content in the urine samples. Hydroxyproline is virtually unique to collagen

which contains approximately 120 microgram of hydroxyproline/ mg of collagen. Present results show that hydroxyproline content increases in rats treated with PTU and carbon tetrachloride whereas it decreases in the urine samples of hyperthyroidic and carbon tetrachloride treated rats. These observations are in agreement with the observations on hepatic collagen, nevertheless, collagen synthesis in altered thyroid status warrants further study.

RESULT

Liver fibrosis is another important pathological manifestation of liver injury caused by several xenobiotics and disease states. Carbon tetrachloride promoted fibrosis in the liver. Thyroidic manipulations as shown by present results affected collagen synthesis and metabolism. A decrease in collagen content was noticed in the liver of carbon tetrachloride treated hyperthyroidic rats, however, an increase was recorded in hypothyroidic and carbon tetrachloride treated rats. It has been shown that collagen metabolism is under the control of an enzyme, collagenase. Furthermore, it was noticed that hydroxyproline content increased in rats treated with PTU and carbon tetrachloride whereas it decreased in the urine samples of hyperthyroidic and carbon tetrachloride treated rats. These observations are in agreement with the observations on hepatic collagen, nevertheless, collagen synthesis in altered thyroid states warrants further study.

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