The Effects of Partial Hepatectomy and Induced Hypothyroidism on the Tissue Lipid Distribution in Rats

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(Received for Publication: September 12, 1969)

ABSTRACT

The nature of the resistance in the rat to the development of experimental atherosclerosis is unknown, and its elucidation on mechanisms is vital to further knowledge of the pathogenesis of the disease. The liver is the main organ where cholesterol synthesis predominantly occurs and is also the main source for the plasma cholesterol. One of the factors which regulates the cholesterol metabolism is the thyroid hormone, that is a well known fact. Therefore, with combination of partial hepectomy and administration of thiouracil, alteration of tissue lipid distribution was studied.

1. Exogenous high cholesterol feeding did not elevate the total serum cholesterol and partial hepectomized rats, but did cause significant alterations in the tissue lipid distribution—particularly in the adrenal gland, small intestine, liver and kidney. The thyroid gland became hyperplastic.

2. The combined administration of Tapazole and cholesterol caused only a slight elevation of the serum cholesterol level as compared with that of controls, but very significant alterations in the tissue lipid distribution in the adrenal gland and liver.

3. The combined administration of Thyroxine and cholesterol caused only a tendency to minimal decrement of serum cholesterol level as compared with that of controls, but produced a significant inhibition of tissue lipid accumulation in the liver and kidney.

4. Partial hepectomy caused neither the changes in serum cholesterol level, nor effect of the tissue lipid distribution.

5. Lipid accumulation in the coronary artery and aorta could not be demonstrated, although there was some alteration in the serum cholesterol level and in the tissue lipid distribution.

It appears that, in the rats, there was no particular alteration of the intestinal absorption of cholesterol regardless of the thyroid status, and in the pathways of cholesterol metabolism after absorption, partial hepectomy did not induce particular effect, but changes in the thyroid function did show measurable effects. However, the fact that there were no significant elevations in the serum cholesterol and tissue lipid in the liver suggests that homeostatic mechanisms may have a greater role in the high resistance to the development of atherosclerosis than does an actively functioning thyroid gland.
cholesterol is the secretion of the endocrine glands (Duell, 1955; Pincus, 1959). The role of the thyroid in controlling the level of plasma lipids and cholesterol is best established, and other endocrine glands such as pituitary, adrenals, gonads, and pancreas also affect the utilization of lipids and cholesterol (Rosenman et al., 1951 & 1952 b; Friedman et al., 1952 a & b; Katz & Stamler, 1953).

The mechanism by which the thyroid hormone affects cholesterol metabolism is not yet known, but there is evidence to suggest that cholesterol destruction is increased in hyperthyroid rats (Byers et al., 1952c). Hence, it is assumed that the thyroid hormone acts on cholesterol metabolism via the liver (Rosenman et al., 1952b).

The liver is the organ where cholesterol synthesis predominantly occurs (Cornforth, 1959), and is the main source for the plasma cholesterol (Friedman et al., 1951 a & b). Although biliary concentration of cholesterol is a reliable index of the rate of hepatic synthesis of this substance (Byers & Friedman, 1952 a & b), cholesterol synthesis may also occur elsewhere (Friedman et al., 1955; Beyer et al., 1956).

This is strongly supported by the fact that the concentration of desmosterol in several tissues may be higher than that observed in the liver and serum. Therefore, the level of circulating cholesterol seems to be regulated by a dynamic interchange of cholesterol between blood and tissue stores (reversible pool), which would depend upon the amount of cholesterol available to the different areas of the body. Induced hypercholesterolemia, when sufficiently prolonged, results in atherosclerosis in many animals. Dogs and especially rats are resistant; resistance in dogs, however, can be overcome by feeding large amounts of cholesterol during induced hypothyroidism (Steiner & Kendall, 1946). The rat is generally considered to be very resistant to development of atherosclerosis, although numerous attempts to produce atherosclerosis in this species have been recorded, most have been completely unsuccessful (Horlick & Havel, 1948; Kendall 1949; Marx et al., 1949; Altschul, 1950; Katz & Stamler, 1953), and the few reported instances of deposition of lipid in rat arteries have apparently had little resemblance to human atherosclerosis (Page & Brown, 1952; Bragden & Boyle, 1952 Wissler et al., 1954; Fillios, et al., 1956).

The nature of this resistance to the development of experimental atherosclerosis is unknown, and its elucidation on mechanisms is vital to further knowledge of the pathogenesis of the disease. One of the factors involved in the process of resistance may be hormonal (Steiner and Kendall, 1946).

Therefore, in rats a few causes for natural resistance may be considered: 1) endogenous destruction of the additional cholesterol; 2) excretion of the additional amount ingested via the bile and the gastrointestinal tract; 3) diminished endogenous synthesis of cholesterol in balance with the additional amount ingested; 4) storage of the additional cholesterol outside the blood stream.

The majority of the studies, particularly in rats, have dealt mainly with the fluctuation of plasma lipid levels and the production of atherosclerosis, but very little attention has been paid to lipid distribution within various organs. Also it is recognized that the level of plasma lipid alone cannot adequately explain the varied features of the diseases resulting from disturbances in lipid metabolism. Therefore, study of the pattern of tissue lipid distribution in hypothyroid and partially hepatectomized (alone or combined) rats seems appropriate and important. Moreover in order to consider the resistance of the production of atheromatous arterial lesions in rats, it is important to evaluate the factors which regulate lipid metabolism.

The purpose of this study is to characterize
the patterns of tissue lipid distribution and define the nature of the morphological changes in various organs in rats, after prolonged administration of high concentration of cholesterol. At the same time, the effect of Tapazole (antithyroid) and of partial hepatectomy was evaluated as to mechanism(s) involved in their action on tissue lipid alterations.

MATERIALS AND METHODS

Healthy male albino rats weighing around 200 Grams were used. A total of 59 rats were subjected to the experiment. The animals were divided into 4 major groups: Group I consisted of 7 rats as normal controls; Group II consisted of 6 rats receiving cholesterol only; Group III consisted of 8 rats receiving cholesterol and Tapazole; Group IV consisted of 38 rats as a partial hepatectomy group. Group IV was subdivided into 5 minor groups: Group "a" consisted of 8 rats receiving partial hepatectomy only as hepatectomy controls; Group "b" consisted of 9 rats receiving cholesterol only after partial hepatectomy; Group "c" consisted of 8 rats receiving Tapazole only after partial hepatectomy; Group "d" consisted of 8 rats receiving cholesterol and Tapazole after partial hepatectomy; Group "e" consisted of 5 rats receiving cholesterol and thyroxine after partial hepatectomy.

Partial hepatectomy was performed by the method of Higgins and Anderson (1931) removing the entire median lobes of the liver, around 40% of the entire liver weight, under ether anesthesia and with aseptic precautions.

Cholesterol was given in 5 gm. per kg. doses daily until the end of the experiment, and Tapazole in 0.17 mg. per kg. doses daily parenterally, and L-thyroxine sodium in 0.2 mg. doses per kg. was given intramuscularly every other day until the end of the experiment.

During the 3 months' experimental period, body weight was measured weekly. The surviving animals were sacrificed at the end of the experimental period. The total serum cholesterol levels were determined by the method of Kingsley and Schaffert (1949). The organs, such as heart, kidney, adrenal, and liver, were weighed. For the study of tissue lipid distribution, Oil Red O stain after frozen sections was performed on the adrenal, small intestine, liver, kidney, heart and the aorta. For the histopathologic examination of the organs, paraffin section of all specimens were prepared.
for hematoxylin-eosin stain and in addition, periodic acid Schiff’s reaction, aldehyde fuchsin stain of Gomori, and the colloidal-Iron method of Rinehart-Abul-Haj, were used for special tissue alterations.

Fig. 3. Change of Organ Weight (1)

Fig. 4. Change of Organ Weight (2)

RESULTS AND DISCUSSION

The level of total serum cholesterol was slightly elevated in the cholesterol-only treated group compared with that of normal controls, and was more elevated in the Tapazole treated groups such as Group II, Group “c” and “d”, compared with that of the cholesterol-only treated group. In contrast, the cholesterol level appeared lower in the thyroxine Treated group than that of the normal controls. In all groups the fluctuation of the cholesterol levels was minimal, and partial heptectomy had no particular effect.

Histopathologic examination of the thyroid showed slight hyperplastic changes in the cholesterol-only treated group with decreased colloid content and increased P.A.S. positive granules in the lining epithelium. The thyroid gland in the Tapazole treated group disclosed marked hyperplasia composed of irregular, small sized follicles with decreased colloid content and also reduced P.A.S. positive granules in the lining epithelium. However, the thyroxine treated group showed intermingled minimal hyperplastic or hypoplastic changes with slightly increased P.A.S. positive granules in the lining epithelium, which appeared to be an effect of cholesterol rather than thyroxine. Bernick et al. (1962) stated that 1% cholesterol diet in several kinds
of animals caused the thyroid glands of hamsters and rats to become hyperplastic, but the glands of rabbits and guinea pigs to become hypoplastic in appearance, and he concluded that the latter animals have a relatively low thyroid activity and their liver is unable efficiently to metabolize exogenous lipids or cholesterol. Hence, they show both hyperlipemia and hypercholesterolemia,
conditions which are factors in their susceptibility to atherosclerosis.

The adrenal gland showed increased sudanophilic material particularly in the zona fasciculata in the cholesterol-only treated group, a finding which was more marked in the Tapazole treated groups and thyroxine treated group, but partial heptatectomy had no particular effect. The

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\text{Table 3. Histologic findings of adrenal gland (1)} & \text{Cortex} & \text{Medulla} \\
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\text{Animal No.} & \text{Zona glomerulosa} & \text{Zona intermediate} & \text{Zona fasciculata} & \text{Zona reticularis} & \text{mitosis} & \text{hyperplasia} \\
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67 & ++ & + & + & + & ± & \\
68 & ++ & + & + & + & + & \\
69 & ++ & + & + & + & + & \\
70 & ++ & + & + & + & + & \\
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\text{Table 4. Histologic findings of adrenal gland (2)} & \text{Cortex} & \text{Medulla} \\
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\text{Animal No.} & \text{Zona glomerulosa} & \text{Zona intermediate} & \text{Zona fasciculata} & \text{Zona reticularis} & \text{mitosis} & \text{hyperplasia} \\
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### Table 5. Fat distribution of small intestine, liver & kidney (1)

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### Table 6. Fat distribution of small intestine, liver & kidney (2)

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The adrenal gland of the thyroxine treated group showed increased mitotic activity in the zona fasciculata, zona reticularis and in the medulla. The small intestine revealed more increased sudanophilic material in the lining epithelium and the stroma of the mucosa in the cholesterol-only treated group, the Tapazole treated groups and the thyroxine treated group, as compared
with normal controls, without significant difference among the groups, and there was also no particular effect following partial hepatectomy. Abell et al. (1966) studied cholesterol metabolism in the dog, and obtained a result of 75 to 83% fecal excretion of administered high cholesterol diet regardless of the thyroid state, but they found no demonstrable effect upon the intestinal absorption of cholesterol. They concluded that the increase in bile acid output was equivalent to the increased cholesterol absorption from the diet. Also it was noted that dogs receiving a high cholesterol diet plus thiouracil have an impaired capacity to convert excess dietary cholesterol into bile acids. In this study, increased sudanophilic material in the intestinal mucosa is considered microscopically to be evidence of increased absorption of cholesterol on the high cholesterol diet. Moreover, it appeared that there were no particular differences in the absorption of cholesterol among the cholesterol-only treated group, the Tapazole treated groups, and the thyroxine treated group.

In the cholesterol-only treated group, the liver showed a minimal degree of sudanophilic material in the Kupffer cells and immediately beneath the hepatic cell membrane particularly around the central veins. In the Tapazole treated groups, sudanophilic material was markedly and diffusely increased throughout the entire lobes, but in the thyroxine treated groups, sudanophilic material had almost completely disappeared.

There were also no significant differences following partial hepatectomy though it appeared to be slightly increased in the hepatectomy groups compared with those of non-hepatectomy groups. Franz et al. (1964) studied the relationship between the level of serum cholesterol and the concentration of hepatic cholesterol. They found a relative constancy of the concentration of serum cholesterol, despite large differences in the cholesterol content of the liver. They postulated the existence of a homeostatic mechanism, and stated that, the liver appeared to act as a buffer for serum cholesterol. So, if large amounts of cholesterol are absorbed from the intestinal tract, the liver quickly removes most of the cholesterol from the blood. As the cholesterol content of the liver rises, hepatic synthesis of cholesterol is depressed. Many investigators have noted the depressed rate of hepatic cholesterol synthesis (endogenous) following the administration of high cholesterol (exogenous) diet in dogs (Gould et al. 1953) and in rats (Tomkins et al., 1953; Frantz et al., 1954). There is a negative feedback mechanism with inhibition of endogenous cholesterol synthesis in the liver following administration of large amounts of exogenous cholesterol.

The kidney showed a minimal degree of sudanophilic material in the renal tubules and glomeruli in the cholesterol-only treated group, and a moderate degree of sudanophilic material in the Tapazole treated groups.

In contrast, in the thyroxine treated groups sudanophilic material was rarely seen. Partial hepatectomy was followed by no significant change nor effect in any of these groups.

The coronary artery and aortas showed neither gross atheromatous changes nor microscopic lipid deposits nor alteration of the acid mucopolysaccharides. However, several instances, particularly of the Tapazole treated groups, showed minimal interruption of the internal elastic membrane in the coronary artery. This appeared to be similar to the coronary artery lesion described by Bernick et al. (1962) who concluded that it was a minimal atherosclerotic lesion despite finding no atheromatous nor lipomatous lesions of the coronary artery. However, in the face of these equivocal findings further studies are needed to prove whether or not actual early atheromatous changes are present.
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LEGENDS FOR FIGURES

Fig. 1. Thyroid gland (Animal No. 54) Group II. The follicles are hyperplastic and increased in number. Their epithelial cells are high cuboidal or tall columnar. H&E stain. 430x.

Fig. 2. Thyroid gland (Animal No. 59) Subgroup "d" of group IV. Follicles disclose marked hyperplasia, increased in number and small in size. Their epithelial cells are tall columnar or high cuboidal. H&E stain. 430x.

Fig. 3. Small intestinal mucosa (Animal No. 51) Group III. This reveals slightly to moderately increased sudanophilic material in the lining epithelium and the stroma of the mucosa. Oil Red O stain. 430x.

Fig. 4. Small intestinal mucosa (Animal No. 60) Group III. This reveals slightly to moderately increased sudanophilic material in the lining epithelium and the stroma of the mucosa. Oil Red O stain 430x.

Fig. 5. Liver (Animal No. 62) Group III. Sudanophilic material is diffusely increased throughout the entire lobe. Oil Red O stain. 430x.

Fig. 6. Liver (Animal No. 9) Subgroup "b" of Group IV. The liver shows sudanophilic material particularly around the central veins. Oil Red O stain. 100x.