Lipotropic Agents and Lipid Transport

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THE term "lipotropic" was first used by Best[1] to describe the action of choline in the prevention and cure of fatty liver. Historically, this term originated from the addition of egg yolk lecithin to the diet of depancreatized dogs in an attempt to prevent the formation of a fatty liver.[2] The identification of choline as the active constituent of the lecithin molecule was established the same year by these investigators.[3] It is of interest that the lipotropic action of choline not only involves the liver, but also other tissues such as the kidney,[4] aorta and blood vessels.[5,6]

The first report of the effects of low protein diet in the production of a fatty liver was reported by Best in 1932.[1,7,8] Tucker and Eckstein showed that the lipotropic constituent of protein was methionine.[9] The role of other amino acids, such as threonine and lysine, in the lipotropic action of methionine has also been investigated.[10] Betaine was reported in 1932 to be an effective lipotropic agent.[4] Inositol,[11] vitamin B_{12} and folic acid,[12] and manganese[13] under certain conditions are active lipotropic agents.

The materials which are physiologically active in removing fat from the liver were shown to be lecithins and choline-containing phospholipids, whereas the cephalins containing ethanolamine were inactive.[4] The composition of liver lipids can be altered by the dietary intake of protein. There is a decrease in the level of total phospholipid in the liver of animals maintained on a low protein diet. This decrease is especially marked in the lecithin fraction.[14] The liver is the main source of phospholipids in the plasma. Plasma phospholipids show a direct reflection of turnover in the liver of the rat,[15] dog[16] and man.[17] The phospholipids of the plasma are primarily choline-containing (70 to 80 per cent).[18] A choline deficiency results in a 30 to 40 per cent decrease in the plasma phospholipids.[19] The synthesis of lecithins in the liver of animals maintained on a low protein diet is approximately the same as in rats maintained on a stock diet,[20] but when guanidoacetic acid[21] or diethanolamine[22] is supplemented in the diet, a marked decrease occurs in the synthesis of lecithins.

Phospholipid synthesis in the liver is a primitive function, and much stress has to be applied if there are to be alterations in this function. The phospholipid synthesis in the plasma of untreated cirrhotic patients[23] or patients with infectious hepatitis[24] is similar to that found in normal persons. The synthesis of liver phospholipid in animals maintained on various diets is constant when expressed as per gram of fat-free tissue,[25] or remains unaltered in the production of dietary cirrhosis. Lipid phosphorylation is greatest in conditions in which a single dose of lipotropic agents is administered in the presence of a fatty liver.[26]

The effect of a dose of choline is chiefly due to the increased rate of formation of lecithins. The stimulating effect of various incomplete methylated ethanolamine derivatives was greatest in lecithin fractions of the liver in rats maintained on a low protein diet.[27] In cirrhotic patients with fatty infiltration in the liver, a significant increase in the rate of phospholipid synthesis was demonstrated by biopsy, after a single oral dose of choline or intravenous administration of methionine.[28] This stimulating effect of lipid phosphorylation by lipotropic agents is somewhat related to the previous diet, for it does not occur

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in experimental animals on a stock diet[29] or in man on an adequate protein intake.[30]

The lipotropic action of choline is primarily involved in the mitochondria and large granules in the liver cell. A decrease occurred in the total lipid and lecithin phospholipids in the liver mitochondria of those animals maintained on a 5 per cent casein diet supplemented with 1 per cent guanidoacetic acid for two weeks.[31] The administration of a single dose of choline (40, 75 or 150 mg.) six hours before sacrificing the animals maintained on a choline-deficient diet produced a significant increase in lecithin phospholipid of the mitochondria. This effect of a single dose of choline (150 mg.) was demonstrated within three, six or ten hours following administration.[32] This observation and that of Artom[33] indicate that mitochondria are primarily involved in the lipotropic mechanism of choline. Lipid analyis of cellular fractions in liver necrosis has demonstrated a decrease in lecithin phosphorus in nuclei.[34]

The lipotropic and lipid phosphorylating effects of choline, betaine and inositol were compared in the liver of rats maintained on low protein-low fat or low protein-high fat diets.[35] All three agents were equally effective in causing a significant reduction of total lipids over controls in animals maintained on the low protein-low fat diet. In rats maintained on the high fat diet, only choline and betaine supplements caused a substantial reduction of total liver fat. Phospholipid synthesis was increased when choline, betaine or inositol was administered as a single dose to animals maintained on the low protein-low fat diet. The order of effectiveness upon turnover rate was choline > betaine > inositol. Both choline and betaine, when administered as single doses, stimulated lipid phosphorylation in rats on the high fat diet, but inositol did not.[35,36] This lipotropic response of choline and betaine was similar to that observed by Young et al.[37] and Morrison.[38] Small doses of methionine are not lipotropic: however, a lipotropic effect was observed in those animals to which threonine was incorporated in the diet along with methionine.[39] It was postulated that methionine stimulates protein metabolism in animals maintained on a low protein diet supplemented with small amounts of this amino acid and therefore methionine fails to exert its lipotropic effect. In order to evaluate this conclusion the uptake of S^{35}-methionine into the sulfur-containing amino acids in liver proteins was studied in rats maintained on diets with and without choline. The evidence presented supports the hypothesis that protein metabolism takes precedence over lipotropic action when animals are subjected to a dietary stress of methyl group deficiency.[40]

Considerable progress has been made in possible pathways of phospholipid synthesis in the liver for partial purified enzyme systems.[41] The *in vivo* effect of coenzyme A, adenosine triphosphate, adenosine-5′-phosphate, cytidine-5′-phosphate and oxalacetate on lipid phosphorylation in the liver of rats has been investigated in choline-deficient rats.[42] A single dose of coenzyme A stimulates phospholipid synthesis in choline-deficient and in pantothenic-deficient animals; oxalacetate stimulates in choline-deficient animals. Administration of a single dose of a mixture of coenzyme A, adenosine-5′-phosphate, oxalacetate and choline stimulates lipid phosphorylation in both mitochondria and nuclei greater than choline. The greatest stimulation occurred in the lecithin fraction. There is considerable evidence that the sulfur-containing amino acids are involved in the production of liver necrosis induced by chemical as well as dietary means. A pronounced decrease in the free sulfhydryl compounds in the liver preceded the production of necrosis. The decreased sulfhydryl concentration occurred in the liver and kidney and to a lesser extent in the heart and spleen.[43]

In order to discuss lipid transport it is necessary to mention the origin and fate of plasma lipids, chemistry of β-lipoproteins, mechanism of hyperlipemia and absorption of lipids. I have already mentioned some facts about the origin and fate of plasma phospholipids. The absolute turnover of phospholipids in man has been reported by Emerson as 18 gm. per day whereas the turnover of cholesterol has been found to be only 1 to 3 gm. Thus, the liver plays a predominant

role in the production and utilization of plasma phospholipids and cholesterol.

SUMMARY

The lipotropic action of choline, betaine, inositol, methionine and dietary proteins is discussed.

The lipotropic action of choline shows its effect not only in the liver but also in other tissues, such as kidney, aorta and other blood vessels. Phospholipids containing choline are involved in this lipotropic process, effecting primarily the mitochondria and large granules in the liver cell.

The effect of a single dose of lipotropic agent is chiefly due to the increased rate of formation of lecithins. In cirrhotic patients with fatty infiltration in the liver, a significant increase in the rate of phospholipid synthesis was demonstrated by biopsy after a single dose of choline or intravenous administration of methionine. This stimulating effect of lipid phosphorylation by lipotropic agents does not occur in experimental animals maintained on stock diet or in man on an adequate protein intake.

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