phatidate rather than on aqueous phosphatidate dispersions (Smith, Sedgwick, Brindley & Hübscher, 1967; Johnston, Rao, Lowe & Schwarz, 1967; Hübscher, Brindley, Smith & Sedgwick, 1967).

The mechanism and exact site of formation of chylomicrons are not fully understood. The enzymes of the glycerophosphate and monoglyceride pathways and CDP-choline-diglyceride cholinephosphotransferase reside in a rough-surfaced vesicle fraction prepared from a total microsomal fraction (Brindley & Hübscher, 1965; Gurr, Brindley & Hübscher, 1965). This membrane system is thus capable of forming triglyceride and phosphatidylcholine, both of which are components of chylomicrons, phosphatidylcholine constituting about 70% of the total phospholipids of chylomicrons (Minari & Zilversmit, 1963). Indications that chylomicrons may be formed in the intestinal mucosa were first provided by Isselbacher & Budz (1963). In this and subsequent investigations (Sabesin & Isselbacher, 1965; Greenberger, Rodgers & Isselbacher, 1966) administration of inhibitors of protein biosynthesis *in vivo* caused an impairment of absorption of long-chain fatty acids with accumulation of higher glycerides in the intestinal mucosa and decreased release of chylomicrons. Similar observations have been made with puromycin (Kayden & Medick, 1969) and carbon tetrachloride (Alpers & Isselbacher, 1968). Further, orotic acid, which interferes with lipoprotein formation in or release from the liver, does not affect the release of β -lipoprotein from the small intestine into the chyle (Windmueller & Levy, 1968) nor the absorption of long-chain fatty acids and subsequent formation of chylomicrons (Kayden, Glassman & Medick, 1969).

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The Role of the Liver in Fatty Acid Transport

By P. A. MAYES. (*Division of Biochemistry, Department of Physiology, Royal Veterinary College, London N.W.1*)

Present interest in the role of the liver in fatty acid transport centres on its interaction with plasma FFA,* on its role in secreting lipoproteins [particularly very-low-density lipoprotein ($d < 1.006$)] and

* Abbreviation: FFA, long-chain non-esterified fatty acids.

in its possible interaction with dietary fat (chylomicrons) and very-low-density lipoprotein. A brief review of these particular aspects will be given, illustrated by experiments of the author and collaborators with the isolated perfused rat liver.

FFA are taken up readily by the liver from the blood. Neither the nutritional state nor variations in concentration of FFA within the physiological range nor variations in availability of glucose have any marked effect on the fractional uptake (Hillyard, Cornelius & Chaikoff, 1959; Mayes & Felts, 1967a). However, the nutritional state has a profound effect on the fate of FFA in the liver. In general, for any given influx of FFA, livers from fed rats esterify more and oxidize less of the influx than do livers from starving rats. Livers from fed animals esterify the greater part of the influx of FFA when the concentration is low. As the concentration of FFA rises, less of the influx is esterified and more is oxidized. This effect of concentration is much less marked, or not seen, in livers from starving animals. As oxidation of FFA increases so does ketogenesis. In isolated mitochondria the production of acetoacetate appears to be under respiratory control, little being formed in uncoupled, compared with tightly coupled, preparations (Shepherd, Yates & Garland, 1966). When high concentrations of ^{14}C -labelled FFA (1.5–2.0 $\mu\text{equiv./ml.}$) are perfused through the isolated liver, more label enters the pathway of ketogenesis and less forms CO_2 . The calculated total yield of ATP resulting from the oxidation of the fatty acid from both pathways remains constant (Mayes & Felts, 1967a). As a low yield of ATP results from the oxidation of fatty acids to ketone bodies, it may be that ketogenesis is a mechanism that allows the liver to oxidize large quantities of fatty acids without necessarily increasing its total production of ATP.

The liver is considered to be the major source of plasma lipoproteins containing triglyceride, cholesterol and phospholipid derived endogenously. Triglyceride is secreted by the liver mainly as very-low-density lipoprotein (pre- β -lipoprotein). The precursors of the triglyceride fatty acids are either FFA or carbohydrate (Fredrickson, Levy & Lees, 1967). The production of very-low-density lipoprotein rises with an increased influx of FFA, but is markedly decreased in the starving state (Heimberg, Weinstein, Klausner & Watkins, 1962; Mayes & Felts, 1967a). The significance of dietary sucrose (or fructose) in raising the concentrations of triglyceride, very-low-density lipoprotein and cholesterol in the plasma has become apparent (Winitz, Graff & Seedman, 1964; Kuo & Bassett, 1965). When [^{14}C]oleic acid-serum albumin complex is infused into the perfused liver in the presence of a circulating concentration of approx. 200mg. of glucose/100ml. of blood, little or no incorporation

of label is found in cholesterol ester. Recently (D. L. Topping & P. A. Mayes, unpublished work) similar experiments have been carried out in the additional presence of a physiological concentration of fructose. These experiments have demonstrated an augmentation of incorporation of label into triglyceride of very-low-density lipoprotein secreted by the liver and a most significant and immediate incorporation into cholesterol ester of liver and of serum lipoproteins of density > 1.006 .

At the present time there is disagreement as to the extent of chylomicron uptake and metabolism by the liver of triglyceride fatty acids. In the whole animal intravenous injection of labelled chylomicrons results in a distribution of 15–35% of the dose in the liver after 10–15 min. (French & Morris, 1958; Bragdon & Gordon, 1958; Borgström & Jordon, 1959; Olivecrona, 1962). Experiments with chylomicrons labelled in the glycerol moiety of the triglyceride with a different isotope from that present in the fatty acid moiety led to the conclusion that triglyceride was taken into liver cells as intact unhydrolysed molecules. Robinson (1963) suggested that at least some of this unhydrolysed triglyceride was present in extracellular spaces within the liver. Experiments with the perfused liver with heparin in the perfusate (see, e.g., Morris, 1963) indicated that 75% of chylomicron triglyceride fatty acids was removed from the perfusate and more than 20% was oxidized to CO_2 and ketone bodies. However, it has been shown that heparin causes active lipoprotein lipase to appear in the perfusate of the isolated liver (Felts & Mayes, 1967). Experiments with the perfused liver without heparin showed little uptake or oxidation of either ^{14}C -labelled triglyceride fatty acids of chylomicrons (Felts & Mayes, 1965) or of very-low-density lipoprotein (Mayes & Felts, 1967b). However, the results of experiments with either liver slices (Ontko & Zilversmit, 1967) or isolated liver cells (Higgins & Green, 1967) have been interpreted as indicating a substantial reaction between chylomicrons and liver cells involving hydrolysis and oxidation and possibly direct uptake of triglyceride. To account for their results *in vivo*, Belfrage (1967) and Schotz, Arnesjö & Olivecrona (1967) suggested that triglyceride trapped by the liver was hydrolysed in the extracellular spaces, liberating FFA. Previously it has not been possible to trap chylomicrons in our perfused liver preparation. Recent experiments (D. F. Tierney & P. A. Mayes, unpublished work) have shown that, on increasing the hepatic venous pressure from a negative pressure to +2 cm. blood, the trapping of chylomicrons during a single passage through the liver increases from about 2% to 10%. When this type of liver preparation was studied for 90 min. with the blood recirculating, oxidation of ^{14}C -labelled triglyceride fatty acids

in chylomicrons remained well below 1% of the total ^{14}C infused.

The support of the Agricultural Research Council and the Medical Research Council is gratefully acknowledged.

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The Use of Fatty Acids by Muscle during Exercise

By LARS A. CARLSON. (*Department of Geriatrics, University of Uppsala, Uppsala, Sweden*)

Muscle tissue may obtain long-chain fatty acids for oxidation from the following sources: (1) plasma lipid transport system: chylomicrons, lipoproteins, free fatty acids; (2) intracellular lipid pools: triglycerides, phospholipids, other (?); (3) local extracellular lipid pools: adipose tissue between muscle fibres. Changes in these different lipid pools during exercise will be reviewed. Quantitative, as well as qualitative, aspects will be covered. Thus in 1965 ten healthy subjects walked 50 km. a day for 10 days. Their daily caloric intake was only about 200 cal. It can be estimated that they spent around 4500 cal./day (3000 for walking and 1500 for basal metabolism) corresponding to 500 g. of fatty acids or 700 g. of adipose tissue. They lost about 0.75 kg./day (Carlson & Fröberg, 1967). The concentration of free fatty acids in the plasma increased to $1.4 \mu\text{moles/ml}$. If we assume the fractional turnover rate of free fatty acids to be about 0.33/min. ($t_{1/2}$ about 2 min.) the value for the concentration of free fatty acids corresponds to a transport of 500 g. of fatty acids from adipose tissue/24 hr. These values support the hypothesis that, in the starving state, free fatty acids are the major transported energy substrate.

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COLLOQUIUM ON 'INTERACTIONS OF NUCLEAR MACROMOLECULES'

Conformations of Nucleohistones and Histones

By E. M. BRADBURY. (*Biophysics Laboratory, Department of Physics, College of Technology, Portsmouth*)

Because of the close association of histones with DNA in the cells of higher organisms, it has been suggested that histones are involved in genetic regulation and much effort has been expended in attempting to demonstrate this role. However, histones are a major component of chromosomes and they could be involved in a purely structural role in controlling the conformational changes that chromosomes undergo during mitosis. Unfortunately there is little precise physical information on the molecular structure of chromosomes and their components and the whole process of chromosomal coiling is not understood.

X-ray-diffraction studies of nucleoproteins have

been disappointing because of the lack of detail in the diffraction patterns. However, a feature of the diffraction patterns that is not present in the diffraction patterns of either the DNA or the total isolated histone is a series of low-angle diffraction rings at 110, 55, 35, 27 and 22 Å (Wilkins, Zubay & Wilson, 1959; Luzzati & Nicolaieff, 1959). From the values of these spacings and their partial meridional orientation, Wilkins (1964) suggested that nucleohistone was in the form of a supercoil of 120 Å pitch and 100 Å diameter. Evidence for this coiled form of nucleohistone has been provided by the experiments of Pardon, Wilkins & Richards (1967) in which a stretched nucleohistone fibre was shown to have lost the low-angle diffraction rings characteristic of the superstructure; the rings, however, reappeared on relaxing the fibre and this cycle could be repeated. It is clear from this experiment that there is a folded structure for