cells were restored towards normal by the superimposed addition of insulin. The adrenaline effect could be mimicked by increasing FFA concentration in the medium.

Possible relationships between lipolysis, FFA concentrations, electrolytes, glucose uptake and energy availability will be discussed (in collaboration with M. Touabi, I. Bihler and J. D. Vassalli).

Transport of Lipid across the Small Intestine

By G. HÜBSCHER. (*Department of Biochemistry, The Medical School, University of Nottingham*)

During the past 10 years a great deal of information has emerged about the mechanism of absorption of fatty acids and glycerides in the small intestine. Most of this information is well documented (see Senior, 1964; Johnston, 1968). The emphasis of this presentation will therefore be on current research in outstanding problems of fat absorption.

One of these is the mechanism of entry of long-chain fatty acids and monoglycerides into the columnar epithelium of the small intestine. After partial hydrolysis of dietary glycerides in the lumen of the small intestine, the liberated long-chain fatty acids and 2-monoglycerides form, with conjugated bile salts, anionic micelles (see Hofmann, 1968). It is in this form that the lipids come into contact with the brush-border membrane.

Although it is generally accepted that micellar lipid is better absorbed than a lipid emulsion, micelles are not an obligatory carrier of lipids across the brush-border membrane. Thus monomolecular solutions of palmitate and oleate are efficiently absorbed (Simmonds, Redgrave & Willix, 1968). This is in agreement with the observation that lipids and bile salts are absorbed individually and not as multiple-component micelles (Thornton, Vahouny & Treadwell, 1968). At variance with these results is the finding that rings of hamster small intestine take up taurodeoxycholate and oleate in approximately equimolar amounts (Gordon & Kern, 1968). Moreover, on the basis of experiments with everted sacs of rat small intestine, Small & Dietschy (1968) have suggested that intact micelles may cross the brush-border membrane. If this were so, bile salts would have to be excreted back into the intestinal lumen because bile salts are absorbed in the lower part (Playoust & Isselbacher, 1964) and fatty acids plus monoglycerides in the upper part (Borgström, Lundh & Hofmann, 1963) of the small intestine.

Theoretical considerations based on the vapour pressure of the solute (Coe, 1966) or on the activation energy required for the passage of lipid from an aqueous to a lipid phase (Danielli, 1964) do not exclude passive transport of lipid across cell membranes (see also Hogben, 1966). Lipid transport is also indicated to be energy-independent

from various experimental studies (Johnston & Borgström, 1964; Strauss, 1966), although the entry is reported to be Na^+ -dependent and to show characteristics typical for a saturation phenomenon (Lyon, 1968). By analogy with the erythrocyte membrane, there is experimental evidence for an energy-dependent entry of palmitate into cell membranes (Shohet, Nathan & Karnovsky, 1968).

The uptake of lipid by the columnar epithelium is of importance as it is the rate-limiting step as compared with the subsequent intracellular biosynthesis of triglycerides (Raghavan & Ganguly, 1967; Hamilton, Webb & Dawson, 1969).

A further topic of current interest is the biosynthesis of triglycerides in the mucosa of the small intestine. The two biosynthetic routes (the glycerophosphate pathway and the monoglyceride pathway; Clark & Hübscher, 1960) have been found by several investigators to occur in the intestinal mucosa of a number of species of laboratory animals. More recently, these pathways have been described in intestinal preparations of chicken, pigs (Bickerstaffe & Annison, 1969) and sheep (Leat & Cunningham, 1968; Bickerstaffe & Annison, 1969).

The monoglyceride pathway is, under normal dietary conditions, the major route of glyceride biosynthesis in rats (Mattson & Volpenhein, 1964; Paris & Clément, 1968) and probably also in man (Kayden, Senior & Mattson, 1967), but only of minor importance in sheep (Bickerstaffe & Annison, 1969). The enzymes catalysing the biosynthesis of triglycerides via the monoglyceride pathway have been purified 70–100-fold from hamster small intestine (Rao & Johnston, 1966). The purified synthetase contained acyl-CoA synthetase, acyl-CoA-monoglyceride acyltransferase and acyl-CoA-diglyceride acyltransferase, which were enriched to approximately the same degree. The purified synthetase, as well as the original microsomal fraction, shows a requirement for enzyme-bound CoA (Rao & Johnston, 1967). Preincubation of the synthetase with palmitoyl-CoA or with ATP, CoA and Mg^{2+} results in the formation of enzyme-bound CoA (or moiety of CoA) that, in a subsequent incubation, can be demonstrated by a CoA-independent biosynthesis of triglyceride from palmitate, monoglyceride and ATP.

Enzyme-bound CoA is also involved in the biosynthesis of triglycerides via the glycerophosphate pathway (Rao & Johnston, 1967). Two further aspects of this pathway should be mentioned. One is related to the role of dihydroxyacetone phosphate as an alternative acyl acceptor, so far described only in subcellular fractions from mammalian liver (Hajra, 1968; Hajra & Agranoff, 1968). The other deals with the requirement for a specific phosphatidate phosphohydrolase, which acts on membrane-bound biosynthetically produced phos-

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

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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.