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Metabolic interactions during pregnancy in preparation for lactation

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1 INTRODUCTION

Gestation is a physiological condition in which the fetus develops at the cost of nutrients crossing the placenta. Among these nutrients, glucose is quantitatively the most important, followed by amino acids (Herrera et al. 1985; Lasunción et al. 1987), and the continuous dependence of the fetus on these compounds is well known. This causes the tendencies in the mother to develop both hypoglycemia and hypoaminoacidemia.

In order to support this continuous extraction of nutrients by the fetus, the mother has to adapt her own metabolism. One of the parameters most affected in the mother is her lipidic metabolism, in spite of the fact that with the exception of ketone bodies and free fatty acids, the placenta is practically impermeable to lipids (Herrera et al. 1990; Herrera et al. 1992a).

Altough it has been long known that the mother accumulates a great proportion of fat depots and develops hyperlipidemia during gestation (Hytten, Leitch, 1971; Beaton et al. 1954), the functional role of such adaptations has not been known until more recently. Now we know, that besides being an alternative source of energy and of gluconeogenetic substrates (Herrera et al. 1992c), these lipids play an essential role in the preparation for lactation. This is the reason why we will analyze here the accumulation of fat depots in the mother during gestation and its physiological consequences, with special emphasis on its role in mammary gland preparation for lactation.

2 MATERNAL BODY FAT ACCUMULATION AND DEVELOPMENT OF HYPERLIPIDEMIA

During gestation, the increase in maternal body weight corresponds not only to the growth of the fetal-placental unit, but to her own structures. The latter is mainly the result of an increase in fat depots, which has been demonstrated both in humans (Hytten, Leitch, 1971) and in the rat (Herrera et al. 1988; López-Luna et al. 1986; Beaton et al. 1954). This change occurs during the first two thirds of gestation (Herrera et al. 1988; Beaton et al. 1954) and has a relationship with the maternal hyperphagia since it disappears with condition of food restriction (Lederman, Rosso, 1980; Moore, Brassel, 1984; Fain, Scow, 1966).

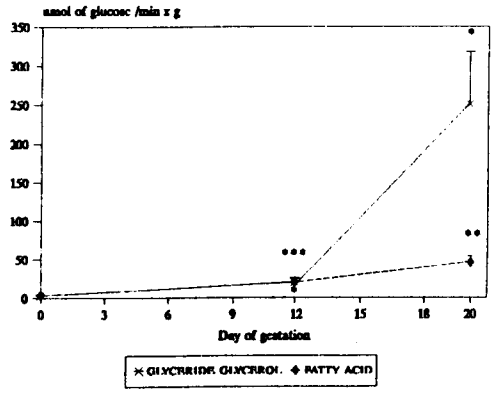

Figure 1.- Fatty acids and glyceride glycerol synthesis by periuterine adipose tissue *in situ* during gestation in the rat. Methodological details have been previously described (Palacín et al., 1991). Values are means ± SEM. Statistical comparisons versus virgin rats (0 days of gestation) are shown by astherisks.

Maternal increase in fat depots is also a consequence of the metabolic changes occurring during the first two thirds of gestation. On the one hand, as shown in figure 1, the synthesis of both fatty acids and glyceride glycerol from glucose in the periuterine fat pad from rats studied *in situ* increases progressively up the 20th day of gestation (Palacín et al. 1991) indicating that triglyceride synthesis is enhanced. On the other hand, we have previously shown that the activity of lipoprotein lipase (LPL) in lumbar fat pads is increased at day 12 of gestation in the rat as compared to virgin controls (Herrera et al. 1992b).

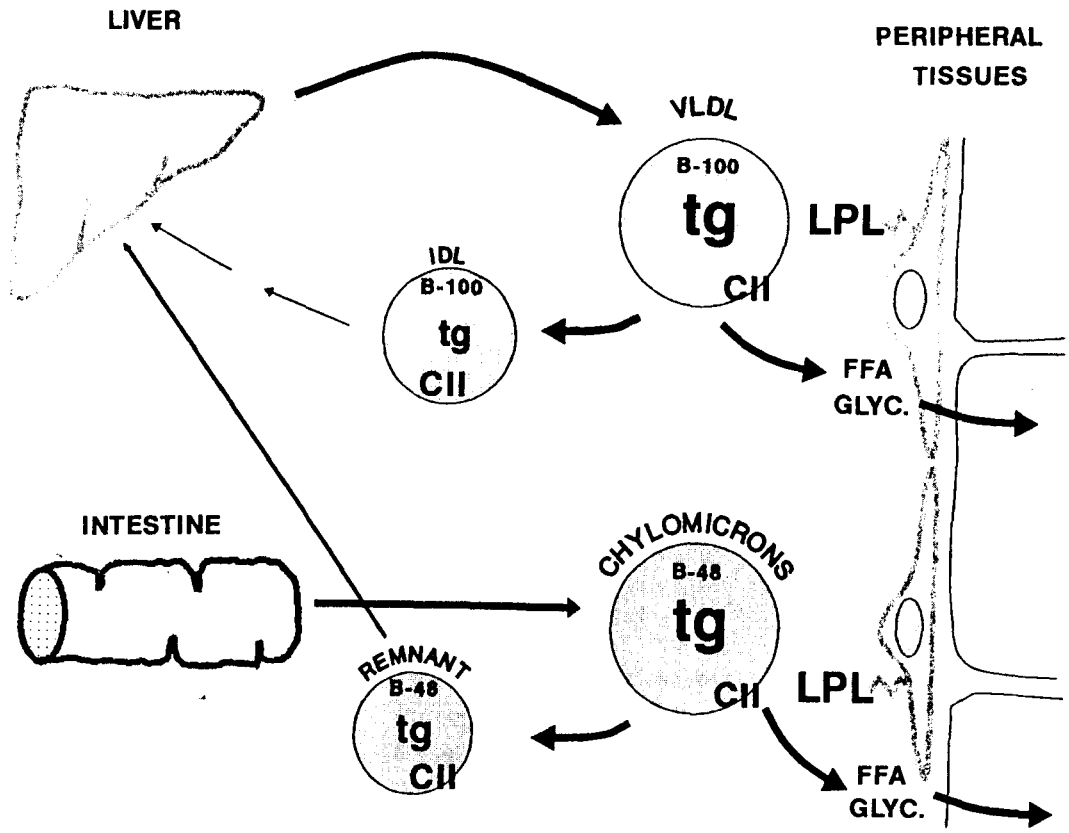

Figure 2.- Role of lipoprotein lipase (LPL) present in the capillary endothelium on the metabolism of triglyceride-rich lipoproteins and the hydrolysis and tissue uptake of circulating triglycerides.

This enzyme is present in the capillary endothelium and hydrolyses the triglycerides that circulate in blood associated to either chylomicrons or very low density lipoproteins (VLDL), which are converted into lipoproteins of higher density, remnants and IDL and LDL respectivelly (figure 2). In this way, LPL facilitates the uptake by the tissue of the hydrolytic products, FFA and glycerol, for their reesterification and storage (Lasunción, Herrera, 1983). The increased activity of LPL found at mid gestation in pregnant rats therefore must also contribute to their fat depots accumulation.

The tendency to accumulate fat in the mother ceases during the last trimester of gestation (Herrera et al. 1988; Hytten, Leitch, 1971; Beaton et al. 1954; López-Luna et al. 1986). This is due to the fact that maternal lipid metabolism switches to a catabolic condition, as shown by an increase in adipose tissue lipolytic activity (Knopp et al. 1970; Chaves, Herrera, 1978) and a reduction in adipose tissue uptake of circulating triglycerides (Herrera et al. 1987) secondary to a decrease in LPL activity (Herrera et al. 1988; Otway, Robinson, 1968; Hamosh et al. 1970; Ramírez et al. 1983). Besides, during late gestation the augmented lipogenetic activity in maternal adipose tissue decreases rapidly (Palacín et al. 1991), and all these changes cause a net accelerated breakdown of the fat depots.

The lipolytic products, free fatty acids (FFA) and glycerol increase in maternal plasma during late gestation (Herrera et al. 1987). The liver is the main receptor organ for these products, where they can be reesterified to be reexported to the circulation in the form of VLDL-triglycerides (Carmaniu, Herrera, 1979). Increased adipose tissue lipolytic activity during late gestation therefore would cause an enhancement in maternal liver VLDL production, which has been directly demonstrated in experimental models (Wasfi et al. 1980; Kalkhoff et al. 1972). This condition is also accompanied by an enhancement in intestinal absorption of dietary lipids (Argilés, Herrera, 1989), all of which causing an exagerated increase in the level of triglycerides in maternal plasma (Knopp et al. 1975; Herrera et al. 1988; Otway, Robinson, 1968; Stemberg et al. 1956; Knopp et al. 1978; Russ et al. 1954; Konttinen et al. 1964; Scow et al. 1964;

Herrera et al. 1969; Argilés, Herrera, 1981).

2.1 Role of the accumulation of body fat during the first half of gestation on maternal hypertriglyceridemia during late gestation

In order to determine how maternal hypertriglyceridemia during late gestation is influenced by the accumulation of fat depots during earlier stages, we studied pregnant rats made diabetics by treatment with streptozotocin (*D*) and receiving a substitution dose of insulin for different periods. Streptozotocin (45 mg/Kg) was given intravenously prior to mating, at which time they were divided into 3 groups: 1) *D-Controls*, which received a daily subcutaneous replacement insulin therapy (1.5 IU/100 g body weight); 2) *D12-20* that received the same treatment from day 0 until day 11th of gestation, and were kept diabetic between days 12 and 20: or 3) *D* that did not receive any treatment throughout pregnancy. All the animals were studied at day 20 of gestation, at which time it was found (Herrera et al. 1990) that the lumbar fat pad weight was much lower in *D* than in *D12-20* rats, whose value was similar to that of *D-Controls*, indicating that diabetes during the first part of gestation, but not during the second, impairs maternal capacity to maintain lipidic maternal stores.

In this same experiment it was found (Herrera et al. 1990) that plasma triglycerides were augmented in *D* and *D12-20* animals as compared to the *D-Controls*, but values in the *D12-20* rats were even higher than in *D*. Since lipidic stores were exhausted in the *D* animals the efficient lipolytic activity required to sustain the endogenous triglycerides overproduction was not possible. We therefore think that this is the reason for *D* rats developing a milder hyperlipidemia than those diabetic animals receiving insulin therapy during the first half of gestation (*D12-20*), where fat depots were built up to the same level as in the *D-Controls*, and therefore were able to sustain a greatly augmented lipolytic activity.

A similar experiment to that for the diabetic rats was carried out by us with thyroidectomized animals. Rats were mated and thyroidectomized on the same day. Some animals were kept without treatment and killed on day 12 or 21 of gestation, whereas others were subsequently treated with L-thyroxine (1.8 ug/100 body weight) for either the first 12 days and then not treated from that time until day 21 or else not treated for the first 12 days and then treated from days 12-21. It was found that (Bonet, Herrera, 1991; Bonet, Herrera, 1988) on day 12 of gestation, maternal net body weight (free of the conceptus), which is an index of the mass of maternal structures, was much smaller in the rats not receiving thyroxine treatment than in those receiving the treatment, and this difference was maintained until the 21st gestational day, even though untreated rats during the first half of gestation received the thyroxyne treatment during the second half, and were euthyroid at the time of sacrifice. All those thyroidectomized rats where the anabolic changes were impaired during the first half of gestation showed a lower hypertriglyceridemia during late gestation, independently of receiving the thyroxine treatment during the second half of gestation (Bonet, Herrera, 1991).

It may be concluded then, that maternal fat store accumulation during the first half of gestation has a pivotal importance on the development of maternal hypertriglyceridemia during late gestation.

3 CONSEQUENCES OF MATERNAL HYPERLIPIDEMIA

These adaptations in maternal lipidic metabolism have important consequences for the mother and her offspring. Both the accumulation of fat depots and the enhaced lipolytic activity in adipose tissue increase glycerol levels in maternal circulation (Chaves, Herrera, 1980). Since the placental transfer of glycerol is much smaller than other hydrosoluble compounds such as glucose or amino acids (Herrera et al. 1992a), the mother uses this metabolite for other pathways. We have shown previously that the conversion of glycerol into glucose in the pregnant rat is even greater than that of the more classical gluconeogenic substrates such as alanine or pyruvate (Herrera et al. 1991; Zorzano, Herrera, 1986; Zorzano et al. 1986). We may therefore conclude, that maternal glycerol actively contributes to the synthesis of glucose that is needed for both placental transfer and maternal tissues. Through this way we see how, in an indirect manner, the fetus benefits from maternal hyperlipidemia, which in fact is greatest during the phase of maximal fetal growth.

Maternal hyperlipidemia may also constitute a "floating" energetic store for both the mother and the fetus, to be used under conditions of a shortage of other nutrients, as in starvation. This reasoning justifies the great ketogenesis that is seen in the late pregnant mother during fasting (Herrera et al. 1969; Scow et al. 1958; Girard et al. 1977). The synthesis of ketone bodies is carried out by the liver from those free fatty acids that are taken up by this organ from both those released to plasma through the lipolytic activity in adipose tissue and those being released

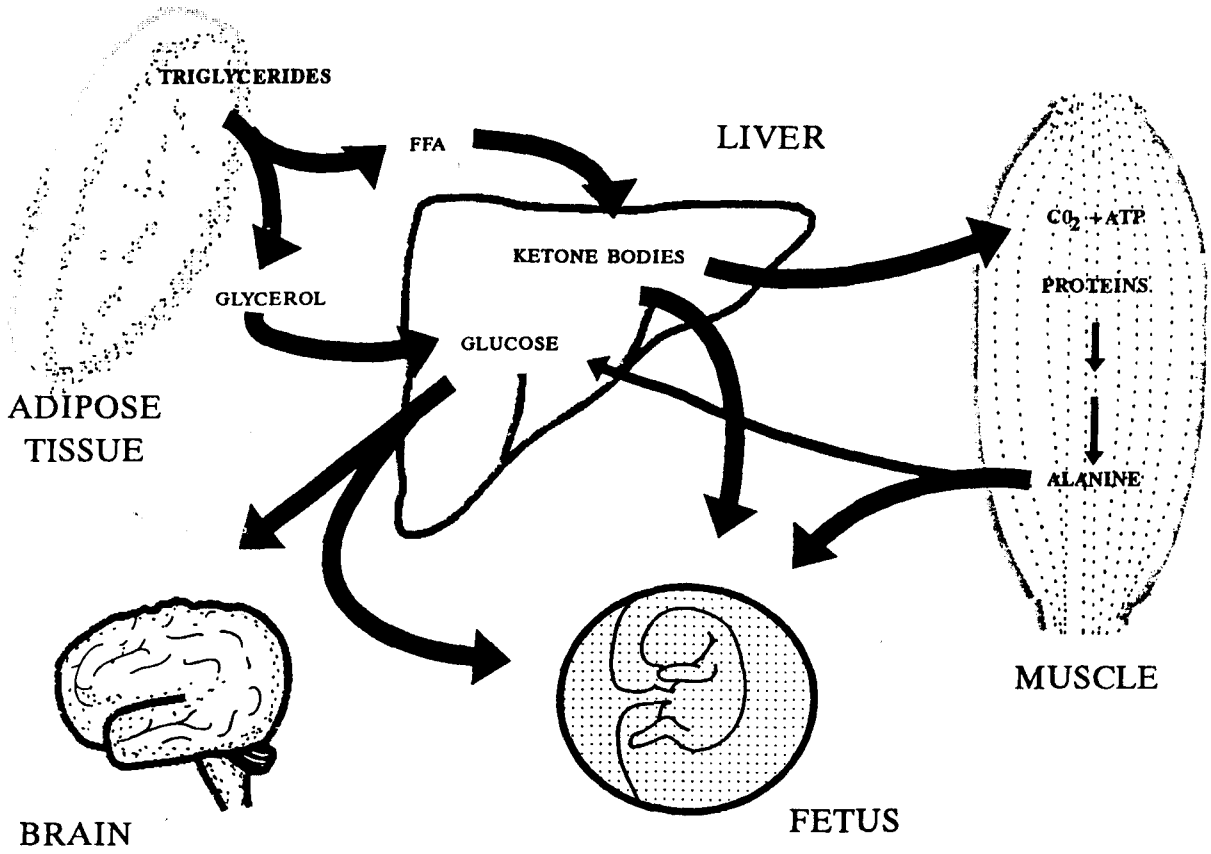

Figure 3.- Role of lipolytic activity in adipose tissue as an important source of substrates for ketogenesis and gluconeogenesis in the fasting condition during late pregnancy, and its consequent availability of metabolites for the fetus.

at the liver capillaries by the action of lipoprotein lipase over circulating triglycerides. We have previously shown that these two processes are greately enhanced in the fasted pregnant rat (Knopp et al. 1970; Chaves, Herrera, 1978; Herrera et al. 1988). The enhanced arrival of ketone bodies to maternal tissues and their use as alternative fuels allows to save other more limited and essential substrates for the fetus, such as amino acids and glucose.

The fetus also receives maternal ketone bodies through the placenta, and their use seems to play an important metabolic role under conditions of maternal nutritional deprivation. Figure 3 summarizes the maternal response to starvation. We see then the important role that maternal fat depots accumulated during early gestation has as main source of substrates for ketogenesis and gluconeogenesis during late gestation, under conditions of food deprivation. In this way, the availability of essential substrates for the fetus is guaranteed.

Despite that maternal hypertriglyceridemia is one of the most striking features of maternal metabolism during late gestation, the transfer of triglycerides through the placenta is practically negligible (Herrera et al. 1992a)). The fetus therefore does not directly benefit from maternal hypertriglyceridemia. As indicated above, the metabolism of circulating triglycerides requires their previous hydrolysis by the LPL action, and with few exceptions, the activity of this enzyme does not change or even decreases in most maternal tissues (Herrera et al. 1988). Within these exceptions is the mammary gland. As shown in figure 4, whereas LPL activity is very similar in 20 pregnant rats and virgin controls in the heart, lung and liver, it is decreased in lumbar fat pads in the former group but it is enhanced in the mammary gland. The functionality of such a change plays an important role in the maternal preparation for lactation, and we therefore should dedicate attention to this specific aspect.

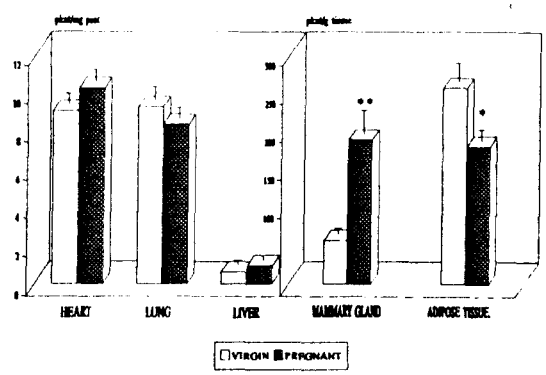

Figure 4.- Lipoprotein lipase activity in different tissues from 20 day pregnant rats and virgin controls. The enzyme activity was measured in acetone-ether extracts, as previously described (Ramírez et al., 1983). Means ± SEM. Statistical comparison versus virgin is shown by astherisks (*).

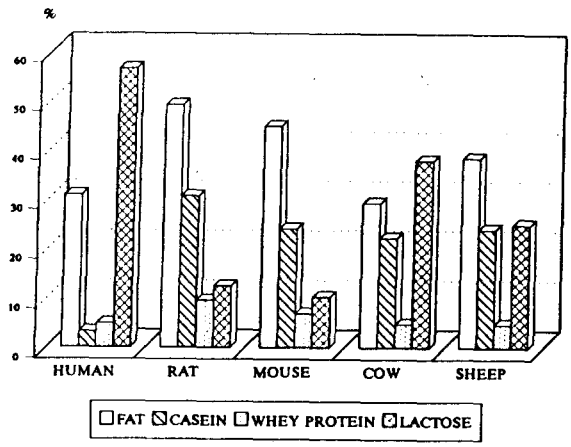

Figure 5.- Percentual distribution of solid components in the milk of different species (adapted from Mepha,. 1976).

4 LIPIDS IN THE MILK AND THEIR SOURCE

As shown in figure 5, in most species lipids are the main solid components of the milk, and even in humans they are so after lactose (Mepham, 1976). Besides, in the suckling infant, maternal lipids constitute up to 50% of the total nutrient calories (Martínez, Dodds, 1983), and they are the vehicule for liposoluble vitamins and essential fatty acids (Ali et al. 1986; Kohn, 1992).

The major components of milk lipids are triglycerides which in human's milk represent up to 98% of the total lipids, whereas phospholipids are just 1% and cholesterol and cholesterol esters around 0.5% (Lammi-Keefe, Jensen, 1984). All this indicates the importance of lipids in the milk and the preponderant role of triglycerides on it.

Milk triglycerides may come from either those synthesized in the mammary gland or those being taken from circulation, which are derived from the diet or from other tissues. From studies in the rat, it is known that the activity of lipogenic enzymes are very low in the mammary gland during gestation and is not induced up to 48 h after parturition (Martyn, Hansen, 1981; Grigor et al. 1982). In spite of low lipogenic activity, as shown in figure 6, the mass of mammary glands and their lipidic content progressively increases from mid gestation and is almost ten times higher prior to parturition (day 21 of gestation in the rat) than in virgin controls. Besides, it is known that the newborns initiate the suckling process before the lipogenic activity of mammary glands becomes fully enhanced (Martyn, Hansen, 1981). This indicates that during the perinatal phase the circulating triglyceride-rich lipoproteins, chylomicrons and VLDLs, constitute the major source for mammary glands triglycerides. This conclusion has been experimentaly supported both in women (Hachey et al. 1987) and in the rat (Ramírez et al. 1983; Argilés, Herrera, 1989).

5 ROLE OF MATERNAL HYPERTRIGLYCERIDEMIA DURING LATE GESTATION ON MILK LIPIDS

Once the importance of circulating triglycerides has as a source of milk lipids around parturition is recognized, we will analyze the role that maternal hypertriglyceridemia has on this, and how they are driven to the mammary gland.

Maternal hypertriglyceridemia disappears around parturition both in women (Miller, 1990; Kallio et al. 1992) and in the rat (Ramírez et al. 1983). This change occurs with minor changes in adipose tissue LPL activity, but it is coincident with an intense and rapid increment in mammary gland LPL activity (Ramírez et al. 1983). Besides, as shown in figure 7, such an increase in mammary gland LPL activity is coincident with an intense increase in the uptake by the same tissue of ^{14}C-lipids 4 hours after an oral load of ^{14}C-tripalmitin to 20 day pregnant rats as compared with virgin rats used as controls. These findings indicate that the induction of LPL activity in the mammary gland during late gestation allows this tissue to increase its capacity to take up circulating triglycerides for milk production.

Since it is known that prolactin is an important

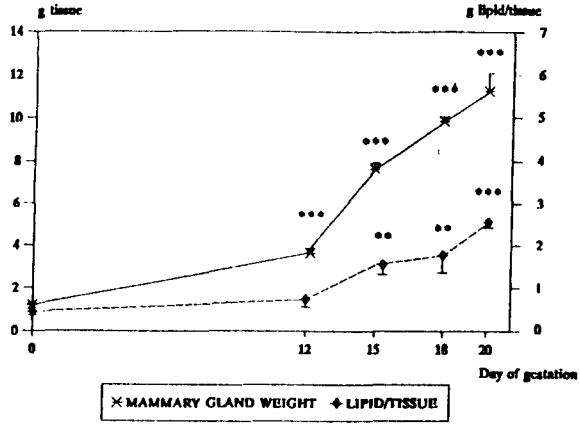

Figure 6.- Fresh weight and lipidic content of mammary glands during gestation in the rat. Experimental protocol was as previously described (López-Luna et al., 1986). Statistical comparison versus virgin rats (0 days of gestation) is shown by astherisks (*).

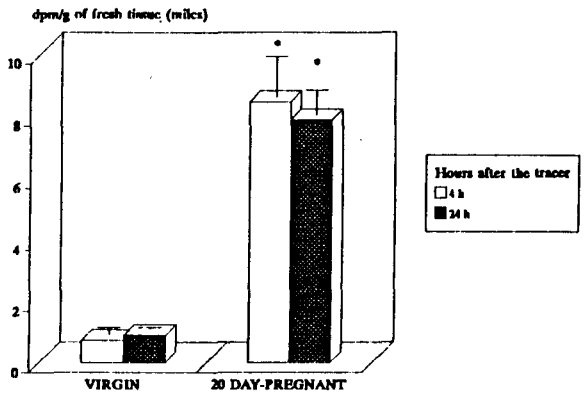

Figure 7.- Appearance of labelled lipids in mammary gland of 20 day pregnant rats and virgin controls at 4 and 24 h after oral administration of ^{14}C-tripalmitate. Experimental details were previously described (Argilés and Herrera, 1989). Means ± SEM. Statistical comparison versus virgin is shown by astherisks (*).

hormonal factor inducing LPL expression in mammary glands around parturition (Spooner et al. 1977), we inhibited the peak of prolactin in the late pregnant rat by giving progesterone treatment and studied its consequences on both mammary gland LPL activity and circulating triglycerides (Ramírez et al. 1983). It was found that progesterone treatment completely inhibits the increase of LPL activity in mammary gland of late pregnant rats and blocks the reversion of maternal hypertriglyceridemia normally occurring in the rat just prior to parturition. These findings, therefore, indicate that besides its role in driving circulating triglycerides to the mammary gland for their uptake, the induction of LPL activity in this tissue plays a key role in the disappearance of maternal hypertriglyceridemia around parturition, a fact that has been well documented both in women (Knopp et al. 1992; Kallio et al. 1992) and in the rat (Ramírez et al. 1983).

Figure 8 summarizes most of these changes occurring in the pregnant mother around parturition: the intense lipolytic activity in adipose tissue facilitates the release of substrates, FFA and glycerol, to the circulation, that are mainly taken up by the liver, where they are reesterified for triglyceride synthesis and reexported into circulation associated to VLDL. These lipoproteins are pooled with those synthesized in the intestine from lipids mainly derived from the diet, chylomicrons, causing an exaggerated increase in the overall total body production of "triglyceride-rich lipoproteins". The decrease in LPL activity in certain maternal tissues, mainly adipose tissue, together with the induction of LPL in the mammary gland drives these lipoproteins to this tissue, where the triglycerides contribute very actively to the synthesis of milk.

6 SUMMARY AND FINAL CONCLUSIONS

On the basis of the above findings it may be concluded that although placental transfer of lipids is small, sustained maternal hyperlipidemia during late gestation is of pivotal importance for the metabolism of the mother and her offspring. Besides aporting essential metabolites to the fetus in an indirect manner, such as glucose synthesized in maternal liver from glycerol released from adipose tissue, the active lipidic metabolism in the mother allows the availability of high amounts of circulating triglyceride-rich lipoproteins for milk synthesis in preparation for lactation. The induction of LPL activity in the mammary gland is important for this function, and warrants the availability of essential fatty acids from the diet to be present in the milk, as well as contributes to the disappearance of maternal hyperlipidemia around parturition. Besides, maternal hyperlipidemia constitutes a floating energetic store to be used under conditions of food deprivation to ensure the availability of alternative substrates for maternal tissues, such a ketone bodies, and to save essential metabolites for the fetus. Maternal hyperlipidemia is the result of numerous and dynamic metabolic adaptations that have to be controlled very finely. Any deviation from this control may alter maternal lipoprotein profile and even be responsible for an alteration in the milk composition, as it has been

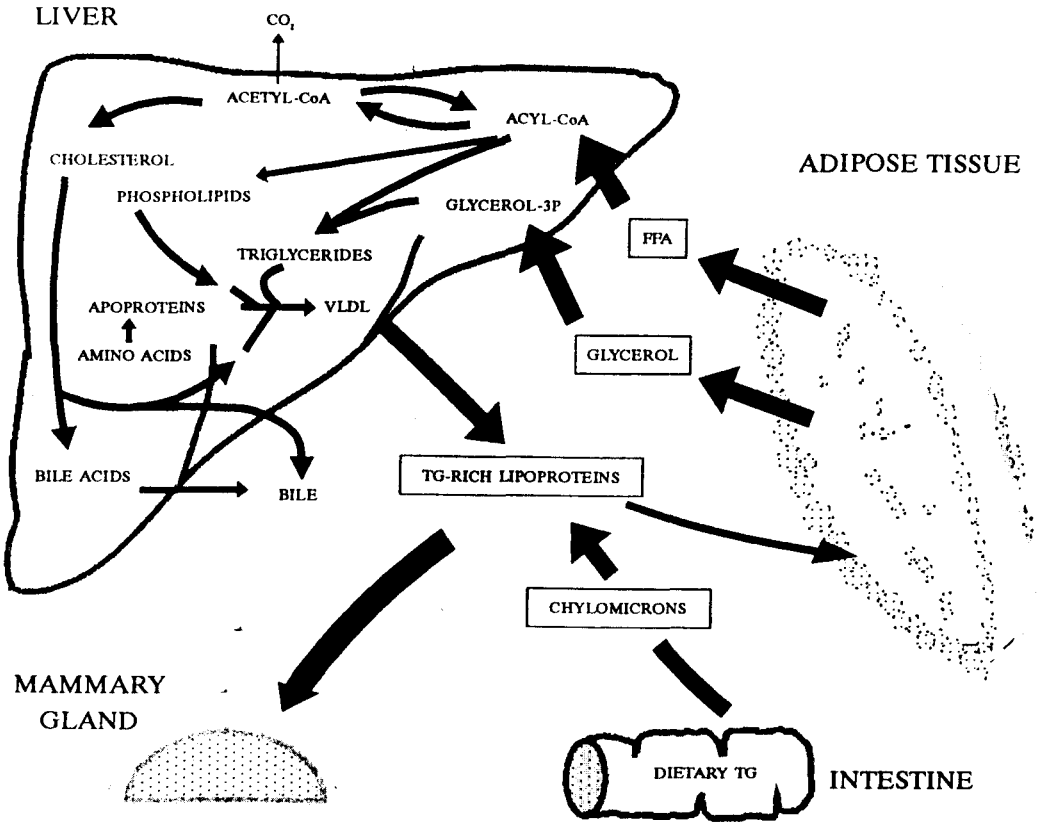

Figure 8.- Summary of the lipidic metabolic interactions around parturition in the pregnant mother.

already reported in dyslipidemic mothers (Myher et al. 1984; Steiner et al. 1985).

7 ACKNOWLEDGEMENT

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