Regulation of lipogenesis in rat tissues during pregnancy and lactation

VICTOR A. ZAMMIT
Hannah Research Institute, Ayr KA6 5HL, Scotland, U.K.

The establishment, maintenance and cessation of pregnancy and lactation are accompanied by a succession of metabolic changes intrinsic to these two physiological conditions but which are superimposed on other, shorter-term (e.g., diurnal) fluctuations. Consequently, a discussion of short-term regulation of metabolism in pregnant and lactating animals is best conducted in the context of these long-term adaptations. Some examples of these interactions within and between different tissues during different parts of the reproductive cycle in the rat are described below.

During pregnancy the metabolism of fatty acids in the liver is diverted primarily towards glycerolipid formation and very-low-density lipoprotein secretion. The hyperglycaemia and hyperinsulinaemia which would be expected from the hyperinsulinaemia which accompanies pregnancy are doubtless related to this direction of liver metabolism, as well as to decreased peripheral lipoprotein lipase activity (Otway & Robinson, 1968). The capacity for hepatic synthesis of fatty acids de novo is also maintained high, as would be expected from the hyperinsulinaemia which develops especially towards the end of the pregnancy (Benito et al., 1982). And yet, the response of the liver to short-term starvation in the (late-) pregnant rat (and other species) is characterized by a more pronounced shift towards fatty acid oxidation and ketogenesis than in the unmated animal (Zammit, 1981). This marked switch in liver metabolism is mediated by several mechanisms that operate both in the liver and in adipose tissue. Lipolysis in the latter becomes more sensitive to glucagon during late gestation; the concentration of glucagon required to elicit half-maximal rates of lipolysis in isolated adipocytes is three-fold lower (N. A. Robson, R. A. Clegg & V. A. Zammit, unpublished work). In the liver there are much larger decreases in mitochondrial glycerol 3-phosphate acyltransferase activity and in malonyl-CoA concentration in the liver of 19–20-day-pregnant animals than in animals in any other reproductive state (Zammit, 1981). The >90% decrease in hepatic malonyl-CoA concentration is achieved through the increased phosphorylation of acetyl-CoA carboxylase as well as through a decrease in enzyme concentration (Zammit & Corstorphine, 1982a). The combined effect of these changes is the de-inhibition of the activity of overt carnitine palmitoyltransferase (CPT I) of liver mitochondria through (i) the decreased direct inhibitory effect of malonyl-CoA on CPT I (Zammit, 1981), (ii) greatly decreased sensitivity of CPT I to malonyl-CoA inhibition (Robinson & Zammit, 1982), (iii) increased hepatic long-chain acyl-CoA concentrations (Zammit, 1981) due to increased mobilization of triacylglycerol from adipose tissue (see above).

Acute changes in metabolism also occur as part of the normal transition from pregnancy to lactation. The last 2 days of pregnancy in the rat are accompanied by a large decrease in the rate of hepatic lipogenesis (Benito et al., 1982). Since this decrease is observed both in vivo and in isolated hepatocytes in vitro (Lorenzo & Benito, 1985) it is likely to be partly a result of a decrease in the concentration of key enzymes of this pathway. Although the relevant studies have not been performed to elucidate these putative changes it is likely that they would include both (pre-) translational and post-translational effects of the sharp fall in the plasma concentrations of insulin that occur during the last 2–3 days of pregnancy. The rate of hepatic lipogenesis recovers even more rapidly after parturition such that on the first day post partum it is completely re-established (Lorenzo et al., 1983). The intriguing aspect of this rapid increase after parturition is that it occurs in spite of the fall in serum insulin concentration that occurs during lactation. Therefore it is necessary to postulate the lipogenic action of another hormone(s) in order to substitute for the normal effect of insulin on the synthesis of lipogenic enzymes in the liver (Nepokroeff et al., 1974). Indeed, the lipogenic capacity of the liver in vivo appears not to operate at maximal capacity during lactation. Thus whereas hepatocytes isolated from lactating rats have a higher lipogenic capacity in vitro than those isolated from unmated animals (Robinson et al., 1978) in vivo the rates of hepatic lipogenesis measured in vivo are very similar for the two conditions (Agus et al., 1979). These observations have led to the suggestion that a systemic factor exists in vivo that depresses hepatic lipogenesis during lactation; prolactin has been proposed to be such a factor (Agus et al., 1979). The validity of this suggestion may be questionable if during lactation the observed rate of lipogenesis in vivo may be limited by the availability of lipogenic substrates rather than by the concentration of any individual enzyme or group of enzymes. This is particularly likely in view of the large substrate requirements by the mammary gland which may compete with those of the liver. Some of the underlying biochemical changes that accompany the high lipogenic and low oxidative profile of the liver during lactation have been described (Zammit, 1980, 1981; Zammit & Corstorphine, 1982a).

Another paradoxical situation exists with respect to the maintenance of a high active/total activity ratio during lactation for one of the key enzymes of fatty acid synthesis in the liver, acetyl-CoA carboxylase (Zammit &
Corstorphine, 1982a), in spite of the very low insulin/glucagon molar ratios that prevail in the portal (Burnol et al., 1983) and peripheral circulations (Robinson et al., 1978). In this respect the amount of active enzyme in the liver appears to bear a closer relationship to the concentration of glucagon than to that of insulin or to the insulin/glucagon concentration ratio. Although the low insulin concentrations would not tend to impair the lipogenic capacity of the liver, they should enable an increased provision of glucose by the liver to the periphery under appropriate conditions (see e.g. Jones & Williamson, 1984).

Interactions between the effects of insulin, glucagon and prolactin (Fig. 1) are important also in effecting the rapid adjustments in the rate of lipogenesis in peripheral tissues that occur on cessation (or even readuction) of food intake by the mother or of sucking by the young. Thus there is a 2-3-fold variation in mammary lipogenesis that accompanies the diurnal rhythm of food intake by the dam (Munday & Williamson, 1983). Similarly, cessation of suckling depresses mammary lipogenesis by >90% in 24 h and increases that in white adipose tissue (Agius et al., 1981). These latter changes can be rationalized by the rapid decline in plasma prolactin concentrations and the concomitant fall in insulin concentrations that occur on weaning. Prolactin maintains fatty acid synthesis de novo in the mammary gland and the activity of lipoprotein lipase in mammary tissue, whereas high concentrations of the hormone are associated with lower values of these parameters in adipose tissue (Zinder et al., 1974; Flint et al., 1981). The surge in insulin concentrations that accompanies weaning would tend to potentiate the increase in adipose tissue synthesis of fatty acids and the uptake of non-esterified fatty acids from the triacylglycerol-rich plasma lipoproteins.

However, the factors that cause the changes in the rate of mammary lipogenesis that accompany short-term food deprivation and refeeding have proved more difficult to identify. Plasma insulin concentrations are known to vary under these conditions (Jones & Williamson, 1984). The rate of lipogenesis in mammary tissue appears to be very responsive to changes in insulin concentration in vivo. This has been demonstrated for the lipogenic pathway as a whole (Jones & Williamson, 1984) as well as for some of its constituent steps, e.g. glucose transport (Threadgold & Kuhn, 1984), acetyl-CoA carboxylase activity (McNeillie & Coore, 1978), and ketone bodies. Such a responsiveness to changes in plasma insulin suggests that the capacity of the gland to respond to insulin is not saturated with the hormone in vivo even in the fed state (Jones & Williamson, 1984). This is presumably partly due to the low insulin concentrations that occur during lactation (see above) and partly by the requirement of some mammary secretory cells for relatively high concentrations of insulin to elicit their lipogenic response. Experimental evidence for the latter suggestion comes from observations of the much lower numbers of insulin receptors in mammary acini compared with, say, adipocytes (Flint, 1982), and the demonstration that the EC50 (concentration of insulin required to give half-maximal stimulation) for insulin stimulated lipogenesis in mammary acini in vitro is 5-10-fold higher than that observed for adipocytes isolated and incubated under the same conditions (N. A. Robson, R. A. Clegg & V. A. Zammit, unpublished work). The combined effect is the optimization of the sensitivity of the response of mammary tissue in vivo to small changes in plasma insulin concentration. Since the sensitivity to insulin of lipogenesis in acini prepared from starved rats is higher than for those from fed rats, it is possible that the rapid increase in the rate of lipogenesis that is observed on refeeding may be partly due to both an increase in insulin concentration and a lower EC50 in the gland. Whether such combined effects can account for the >80% decrease in lipogenic rate that occurs after 6 h starvation, or for its rapid recovery after 2 h refueling, cannot be ascertained at present. Other factors, some of which are known (e.g. changes in mammary blood flow, availability of ketone bodies), must also be involved. Currently unidentified factors could include gastrointestinal hormones and metabolites (other than ketone bodies) capable of affecting mammary lipogenesis. In this respect it is instructive to note that (i) the rate of glucose uptake by the mammary gland recovers during refeeding faster than either lipogenesis or lactose synthesis (Threadgold & Kuhn, 1984), and (ii) that synthesis of lactose and lipid in the mammary gland may compete for intracellular glucose (Burnol et al., 1985).

The search for additional factors that antagonize the action of insulin, and that may decrease during refeeding thereby amplifying the response of the gland during to the hormone, has necessarily involved the screening of several hormones for their possible inhibitory action on lipogenesis in mammary tissue. Teleologically a hormone such as glucagon would be expected to have such a function since the circulatory concentration of glucagon is related to dietary intake. However, this hormone was found to have no effect on the rate of lipogenesis in mammary acini; nor did it affect the does-response curves for the effect of insulin on lipogenesis (Robson et al., 1984). The reason for this lack of effect was established as being the lack of receptors for glucagon in mammary secretory cells (Robson et al., 1984). This is an important physiological strategy that complements the low sensitivity (high EC50, see above) of mammary tissue towards insulin. What has aroused interest in this lack of effect of glucagon is the relatively recent finding that glucagon, at near-physiological concentrations, could have an anti-lipogenic effect in adipose tissue (Zammit & Corstorphine, 1982b; Robson et al., 1984; Holland et al., 1985). During lactation this anti-lipogenic action of glucagon on adipose tissue would reinforce the effects of the high concentration of prolactin and low concentration of insulin in the plasma (outlined above). In addition,
sensitivity of adipose tissue to glucagon would enhance the lipolytic response of adipose tissue (already favoured by the maintenance of low plasma insulin concentrations) at a time when the triacylglycerol stores of the tissue may be required to supply pre-formed fatty acids to the mammary gland. Indeed the sensitivity to glucagon of lipolysis in adipocytes isolated from mid-lactating rats is significantly higher than in those isolated from either unmated or early-lactating rats (N. A. Robson, R. A. Clegg & V. A. Zammit, unpublished work). Thus, during lactation, whereas the lipolytic profile of adipose tissue is maintained by the low insulin/glucagon concentration ratio, the lipogenic response of mammary tissue to changes in plasma insulin concentrations is unimpaired by this ratio because of the complete insensitivity of mammary tissue to glucagon (see Robson et al., 1984).