

Fatty acid oxidation and ketogenesis during development

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Summary. Fatty acids are the preferred oxidative substrates of the heart, skeletal muscles, kidney cortex and liver in adult mammals. They are supplied to these tissues either as non-esterified fatty acids (NEFA), or as triglycerides after hydrolysis by lipoprotein lipase. During fetal life, tissue capacity to oxidize NEFA is very low, even in species in which the placental transfer of NEFA and carnitine is high. At birth, the ability to oxidize NEFA from endogenous sources or from milk (a high-fat diet) develops rapidly in various tissues and remains very high throughout the suckling period. Ketogenesis appears in the liver by 6 to 12 hrs after birth, and the ketone bodies are used as oxidative fuels by various tissues during the suckling period. At the time of weaning, the transition from a high-fat to a high-carbohydrate diet is attended by a progressive decrease in the ketogenic capacity of the liver, whereas other tissues (skeletal muscle, heart, kidney) maintain a high capacity for NEFA oxidation. The nutritional and hormonal factors involved in changes in fatty acid oxidation during development are discussed.

Introduction.

In adult mammals, fatty acids are the major oxidative fuel of the body in the post-absorptive period and during fasting, cold exposure and the consumption of a high-fat diet. The principal organs responsible for fatty acid oxidation are the heart, skeletal muscles, liver and kidney cortex. Fatty acids are supplied to these tissues from the blood as non-esterified fatty acids (NEFA) bound to albumin or as triglycerides in chylomicrons and very-low-density lipoproteins. Prior to their utilization in extra-hepatic tissues, the triglycerides are hydrolysed to NEFA by lipoprotein lipase. Although quantitative information on the direct contribution of triglyceride fatty acids to oxidative metabolism is lacking in adults, it is generally accepted that the bulk of the fatty acids oxidized reach the tissues in the form of NEFA (Robinson, 1969 ; Krebs, 1972).

Before considering the cellular aspects of fatty acid oxidation during development, it would be useful to review briefly the pathway involved in fatty acid oxidation in adult tissues. The mechanisms involved in the uptake of NEFA by the cells are unclear but they may depend upon specific transport systems.

However, it appears that this process is energy-independent and functions to maintain an equilibrium between the plasma and the cellular pools of NEFA (Spector, 1971). Once inside the cell, NEFA are bound to fatty acid binding protein (FABP) (Ockner *et al.*, 1972) which delivers long-chain fatty acids to their sites of activation to fatty acyl-CoA (FACoA) by acyl-CoA synthetases (fig. 1). Fatty acids with a chain length of more than 12 carbons are activated to their

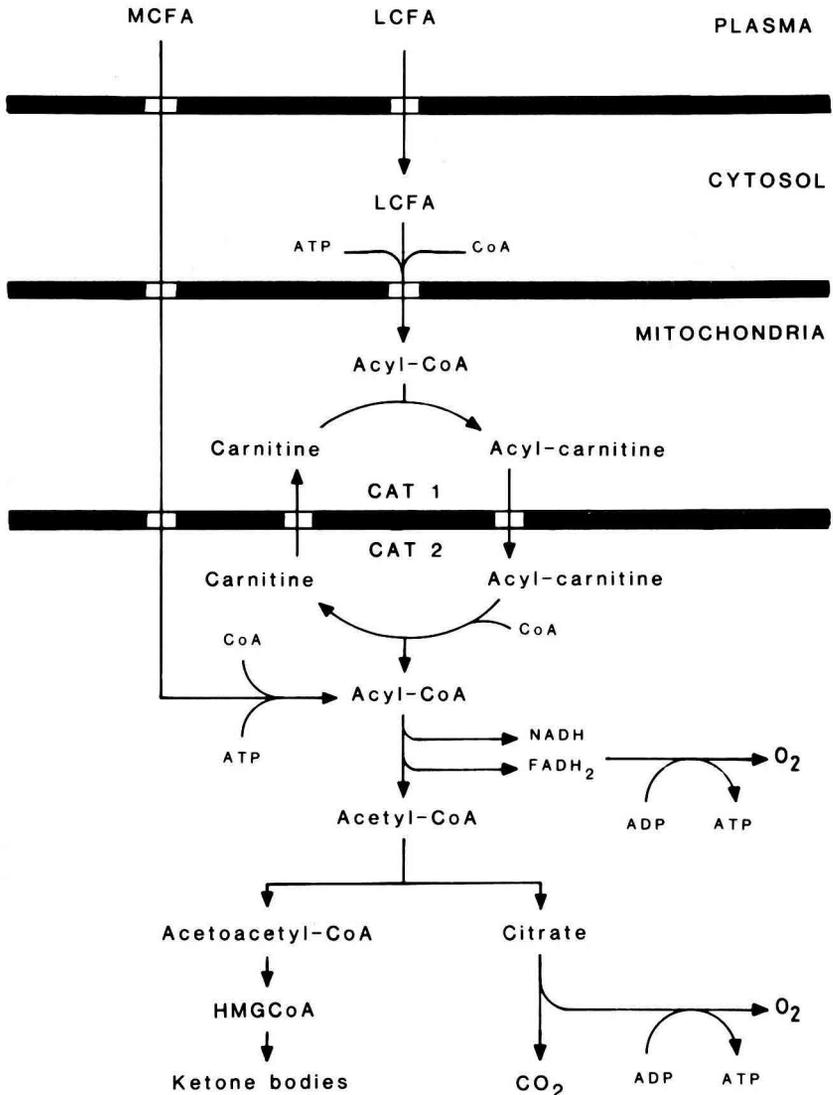


FIG. 1. — Pathway of fatty acid catabolism. LCFA : long-chain fatty acids ; MCFA : medium-chain fatty acids ; CAT I and CAT II : carnitine acyltransferase I and II. The acetyl-CoA can be oriented towards CO₂ or ketone body synthesis. See text for further details.

corresponding acyl-CoA in the cytosol by acyl-CoA synthetases located on the microsomes and the outer mitochondrial membrane (Bremer and Osmundsen, 1984). The microsomal enzyme could be involved in providing acyl-CoA for esterification, whereas the mitochondrial enzyme could provide acyl-CoA for oxidation. It is not known whether these enzymes share a single pool of long-chain fatty acids or whether incoming fatty acids are directed to either the mitochondrial or microsomal enzyme, depending on the physiological state. As the inner mitochondrial membrane is impermeable to CoA and acyl-CoA, a specific transport system is required for the transfer of long-chain acyl-CoA into the mitochondria for oxidation. This transfer involves the sequential action of two carnitine acyltransferases (see Bremer, 1983). Carnitine acyltransferase I (CAT I), located on the outer side of the inner mitochondrial membrane, catalyzes the synthesis of acylcarnitine esters which are then translocated through the inner membrane into the matrix of the mitochondria by carnitine-acylcarnitine translocase (fig. 1). Carnitine acyltransferase II (CAT II), located on the inside surface of the inner mitochondrial membrane, transforms acylcarnitine esters into the corresponding long-chain acyl-CoA which is oxidized in two stages by specific enzymes located in the mitochondrial matrix. In the first stage, acyl-CoA undergoes β -oxidation which generates acetyl-CoA and reduced equivalents (NADH and FADH_2). In the second stage, acetyl-CoA is oxidized via the citric acid cycle to yield CO_2 , H_2O , GTP and further reduced equivalents. These reduced equivalents may enter the respiratory chain to yield ATP (fig. 1).

In contrast to long-chain fatty acids, short or medium-chain fatty acids (chain length of less than 10 carbons) readily traverse the mitochondrial membranes and are activated to their corresponding acyl-CoA by a short or medium-chain acyl-CoA synthetase located in the mitochondrial matrix. Short and medium-chain acyl-CoA then undergo β -oxidation as do long-chain acyl-CoA. The metabolic fate of acyl-CoA in mitochondria is different in liver than in extra-hepatic tissues. In the mitochondria of heart, skeletal muscles and kidney cortex the final products of fatty acid oxidation are CO_2 , H_2O and ATP; in the mitochondria of liver a part of the acetyl-CoA produced by β -oxidation is used for ketone body synthesis (fig. 1). These ketone bodies are then released into the circulation and carried to the extra-hepatic tissues where they are completely oxidized (see Robinson and Williamson, 1980; Williamson, 1982).

It has been demonstrated recently that fatty acid oxidation can also occur in peroxisomes (Lazarow and De Duve, 1976). However, there are several important differences between the mitochondrial and peroxisomal pathways: (1) the first enzyme of peroxisomal β -oxidation is an acyl-CoA oxidase that transfers electrons directly to O_2 and generates H_2O_2 ; (2) peroxisomes do not completely oxidize acyl-CoA to acetyl-CoA; acyl-CoA shorter than octanoyl-CoA are not oxidized and are exported out of the peroxisomes into the mitochondria for oxidation; (3) peroxisomal fatty acid oxidation is not coupled to the respiratory chain; (4) carnitine is not required for the transport of long-chain acyl-CoA across the peroxisomal membrane (see Debeer and Mannaerts, 1983). The experimental evidence presently available indicates that peroxisomal β -oxidation plays a minor role in overall fatty acid oxidation in both adult (Debeer and Mannaerts, 1983) and

newborn (Krahling *et al.*, 1979 ; Horie, Ishii and Suga, 1981) rats. Only mitochondrial fatty acid oxidation will be discussed in the following paragraphs.

Several factors may be involved in the development of fatty acid oxidation in individual tissues : (1) the supply of fatty acids and carnitine, (2) the activity and amounts of various enzymes of fatty acid oxidation and ketogenesis and (3) the presence or absence of specific cofactors or hormones involved in the regulation of these metabolic pathways. The aim of the present paper is to review the changes in fatty acid oxidation that occur in mammals at two crucial steps in their development, *i.e.* during fetal-neonatal transition and during suckling-weanling transition. Several reviews on this subject have been published previously (Bailey and Lockwood, 1973 ; Warshaw, 1979 ; Williamson, 1982).

A. Supply of fatty acid and carnitine during development.

The fetus of most mammals is devoid of adipose tissue at term (see Girard and Ferré, 1982), and the NEFA present in fetal plasma are derived from the maternal circulation. The facility with which NEFA cross the placenta varies considerably from one species to another. It occurs currently in those species with sizeable lipid stores at birth, *e.g.* humans, guinea-pigs and rabbits, but not in those with limited lipid stores, *e.g.* sheep, pigs and rats (see Girard and Ferré, 1982). Carnitine is a necessary cofactor in the optimal transfer of long-chain fatty acids across the mitochondrial membranes and hence could play an essential role in regulating fatty acid oxidation and ketone body formation. In both the liver and kidney of adults, carnitine is synthesized from the essential amino acids, lysine and methionine (see Bremer, 1983). Since the fetus has a very limited ability to synthesize carnitine (Hahn, 1981), it is entirely dependent upon the placental transfer of maternally-derived carnitine. In rats and sheep the placental transfer of carnitine is poor (Hahn and Skala, 1975 ; Hahn *et al.*, 1977), as is the transport of NEFA, and it is not surprising that fatty acids do not contribute significantly to fetal oxidative metabolism (Battaglia and Meschia, 1978 ; Girard, Pintado and Ferré, 1979 ; Girard and Ferré, 1982). In rabbits and guinea-pigs the placental transfer of both carnitine (Hahn, Seccombe and Towell, 1981) and NEFA is rapid but, despite an adequate supply of these, the fetal tissues do not oxidize fatty acids. The reasons for this will be discussed below.

Immediately after birth and throughout the suckling period newborn mammals are fed with milk which, in most species, is a high-fat, low-carbohydrate diet (Jenness, 1974). More than 90 % of milk fat is in the form of triglycerides and, in many species, they contain significant amounts of medium-chain fatty acids (Dils and Parker, 1982). Whereas long-chain fatty acids are absorbed from the small intestine as chylomicrons, medium-chain fatty acids are absorbed from the stomach as free acids (Hamosh, 1979 ; Fernando-Warnakulasuriya *et al.*, 1981 ; Aw and Grigor, 1980) and, as such, are excellent oxidative substrates for neonatal tissues, particularly for the liver (Frost and Wells, 1981). In rats, a large rise in plasma NEFA and triglyceride occurs a few hours after birth with the onset of suckling, and plasma NEFA and triglyceride levels

remain very high throughout the suckling period, decreasing after weaning (Page, Krebs and Williamson, 1971 ; Dahlquist, Persson and Persson, 1972 ; Foster and Bailey, 1976a ; Planche *et al.*, 1980). The capacity of extra-hepatic tissue to take up plasma triglycerides increases during the suckling period in rats. The lipoprotein lipase activity of heart, skeletal muscles and brown adipose tissue (BAT) emerges substantially during the first 24 h after birth (Cryer and Jones, 1978) and remains elevated during the suckling period (Cryer and Jones, 1978 ; Planche *et al.*, 1980). The NEFA released by the hydrolysis of plasma triglycerides are thus directly available as fuel for the extra-hepatic tissues. After birth, carnitine concentration increases markedly in heart, skeletal muscles, BAT and liver with the onset of suckling (Robles-Valdes, McGarry and Foster, 1976 ; Borum, 1978 ; Hahn and Skala, 1972 ; Bieber *et al.*, 1973 ; Carroll *et al.*, 1983). As newborn rats have a low ability to synthesize carnitine during the first postnatal week (Hahn, 1981), it is synthesized in the liver of the lactating dams and then transferred to the pups via the milk (Robles-Valdes, McGarry and Foster, 1976). Thus, the supply of NEFA and carnitine to neonatal tissues is very high during the suckling period and can maintain the capacity for fatty acid oxidation at a high level.

The transition from milk to chow is gradual in laboratory animals, and weaning is characterized by a change from a high-fat/low-carbohydrate diet to a high-carbohydrate/low-fat diet (Henning, 1981). The intestine progressively becomes the more important site of dietary fat absorption and digestion when pancreatic lipase appears, long-chain fatty acids being absorbed via the lymphatic ducts as chylomicrons, as in adults, (Hamosh, 1979 ; Henning, 1981). Weaning in rats is associated with a decrease in plasma NEFA and triglyceride levels (Foster and Bailey, 1976a). After weaning, lipoprotein lipase activity remains high in heart but decreases markedly in skeletal muscles and BAT (Cryer and Jones, 1978). In contrast, kidney lipoprotein lipase activity, which is low during the suckling period, increases to reach adult values one week after weaning (Planche *et al.*, 1980). Thus, the suckling-weaning transition is characterized by a decrease in the supply of fatty acid to the tissue of fed young and adult rats.

B. Development of fatty acid oxidation in extra-hepatic tissues.

In vitro studies using tissue homogenates (Warshaw, 1972 ; Glatz and Veerkamp, 1982 ; Wolfe, Maxwell and Nelson, 1978), isolated mitochondria (Warshaw and Terry, 1970 ; Werner *et al.*, 1982) or isolated perfused organ (Werner *et al.*, 1983b) have shown that the heart of fetal rats, rabbits, pigs and calves has a very low capacity for long-chain fatty acid oxidation, even in the presence of carnitine. Similarly, compared to adults, the rate of palmitate oxidation is reduced in skeletal muscle homogenates (Glatz and Veerkamp, 1982 ; Carroll *et al.*, 1983 ; Wolfe, Maxwell and Nelson, 1978 ; Mac Larty *et al.*, 1984) and in kidney slices (Wolfe, Maxwell and Nelson, 1978 ; Freund, Sedraoui and Geloso, 1984), lung (Warshaw, Terry and Ranis, 1980) and small intestine (Warshaw, 1974) of fetal rats and pigs. As the rate of oxidation of octanoate,

octanoylcarnitine or palmitoylcarnitine is similar in the heart of fetal, newborn and adult pigs and calves (Werner *et al.*, 1983a, b ; Warshaw and Terry, 1970), it has been suggested that the reduced capacity of the fetal tissues to oxidize long-chain fatty acids could result from the low activity of carnitine acyltransferase I (Warshaw, 1972 ; Carroll *et al.*, 1983 ; Delaval *et al.*, 1984). Moreover, a reduced number of mitochondria in fetal tissues could also be responsible for their low capacity to oxidize NEFA (Warshaw, 1972 ; Glatz and Veerkamp, 1982 ; Barrie and Harris, 1977).

The capacity of heart (Wittels and Bressler, 1965 ; Warshaw and Terry, 1970 ; Warshaw, 1972 ; Mersmann and Phinney, 1973 ; Aprille, 1976 ; Wolfe, Maxwell and Nelson, 1978 ; Werner *et al.*, 1982, 1983a), skeletal muscle (Wolfe, Maxwell and Nelson, 1978 ; Glatz and Veerkamp, 1982 ; Carroll *et al.*, 1983) and kidney (Wolfe, Maxwell and Nelson, 1978 ; Freund, Sedraoui and Geloso, 1984) to oxidize NEFA increases shortly after birth in rats, rabbits, pigs and calves. In contrast, it has been reported that substantial fatty acid oxidation occurs only 2 weeks after birth in dog heart (Breuer *et al.*, 1968). Rosenthal and Warshaw (1977) have reported that fatty acid oxidation remains very low in heart cells isolated from 15-day old fetal rats and cultured for a period of time (6-12 days) which spans the expected perinatal rise in fatty acid oxidation. This provides indirect evidence that birth-associated changes are regulated and are not the result of a predetermined program. It also seems that the transition to a high-fat diet is not a prerequisite for the increased ability to oxidize fatty acid in neonatal tissues. Indeed, young rabbits or piglets maintained on low-fat diets develop a normal capacity to oxidize fatty acids in heart, skeletal muscle and kidney (Aprille, 1976 ; Wolfe, Maxwell and Nelson, 1978).

In general, the rise in the capacity of the extra-hepatic tissues to oxidize fatty acids varies in parallel with CAT activity. A rise in this activity occurs immediately after birth in the heart (Wittels and Bressler, 1965 ; Warshaw, 1972 ; Lockwood and Bailey, 1970 ; Barrie and Harris, 1977), skeletal muscle (Carroll *et al.*, 1983), lung (Warshaw, Terry and Ranis, 1980) and kidney (Delaval *et al.*, 1984) of rats and remains elevated throughout the suckling period. However, CAT activity does not change with age in the heart, leg muscles and kidney of pigs, although palmitate oxidation increases 2 to 3-fold (Wolfe, Maxwell and Nelson, 1978). The increase in the number of mitochondria that occurs after birth in the extra-hepatic tissues (Warshaw, 1972 ; Barrie and Harris, 1977 ; Glatz and Veerkamp, 1982) is obviously a factor in the increased capacity for fatty acid oxidation.

After weaning, this capacity remains elevated in heart (Warshaw, 1972 ; Glatz and Veerkamp, 1982 ; Werner *et al.*, 1982), kidney (Novakova *et al.*, 1980 ; Freund, Sedraoui and Geloso, 1984) and, to a lesser extent, in skeletal muscles (Glatz and Veerkamp, 1982 ; Carroll *et al.*, 1983). This is not surprising since it is well known that NEFA are the preferred fuel of adult heart, kidney and resting muscles (see review by Owen and Reichard, 1974).

C. Development of fatty acid oxidation and ketogenesis in the liver.

A number of mechanisms have been proposed to explain the increased rate of fatty acid oxidation and ketogenesis in adult rats during starvation and diabetes

(McGarry and Foster, 1980). These include increased delivery of fatty acids to the liver, an enhanced plasma glucagon : insulin ratio, a rise in hepatic carnitine level, and a fall in liver malonyl-CoA (the first committed intermediate in hepatic lipogenesis which is a powerful inhibitor of CAT I) that initiates the carnitine acyltransferase reaction (McGarry and Foster, 1980). These different factors and their involvement in the development and regulation of hepatic fatty acid oxidation and ketogenesis will be considered in the following discussion.

1. Fetal-neonatal transition.

a) *Increased fatty acid availability.* — During the neonatal period, the NEFA supplied to the liver originate from two different sources : (1) triglycerides stored in white adipose tissue or liver and (2) milk triglycerides. The importance of endogenous triglycerides as ketone body precursors can be studied in starved newborns. Newborn guinea-pigs and rabbits which have very little white adipose tissue and large fat stores in the liver develop a marked hyperketonemia after 12-24 h, if they are not fed from birth (Callikan *et al.*, 1979 ; Duée *et al.*, 1983). In these species, NEFA provided by hepatic triglyceride breakdown are the major precursors of ketone bodies during starvation. In keeping with this, it has been shown that several drugs which inhibit lysosomal acid triglyceride lipase completely suppress the endogenous production of ketone bodies by isolated hepatocytes from starved newborn rabbits (Duée *et al.*, 1985).

Newborn human babies which are endowed with significant fat stores in both the liver and white adipose tissue also show an increase in blood ketone body levels when they are starved from birth (Melichar, Drahota and Hahn, 1965 ; Haymond, Karl and Pagliara, 1974) ; the NEFA used for ketone body production are derived from both the adipose tissue and the liver.

In contrast, newborn rats which have no fat stores at birth remain hypoketonemic if they are starved from birth (Girard *et al.*, 1973). Thus, efficient ketogenesis in these animals appears to be entirely dependent upon NEFA provided by hydrolysis of milk triglycerides (Ferré *et al.*, 1978). In suckling rats blood ketone body concentrations increase slowly during the first 12 h after birth, despite the large increase in plasma NEFA which occurs 2 h after birth. Blood ketone bodies then increase sharply between 12 and 16 h without any further rise in plasma NEFA levels (Ferré *et al.*, 1978). A similar pattern in the ketogenic capacity of newborn rats is observed when starved newborns are fed with a triglyceride emulsion containing long-chain fatty acids (Ferré *et al.*, 1978) or medium-chain fatty acids (unpublished data) at different times after birth. This suggests that factors other than NEFA availability alone are responsible for the onset of ketogenesis in newborn rats (Ferré *et al.*, 1978). Similarly, a delay of 6 to 12 h in the appearance of hyperketonemia has been observed in suckling rabbits (Girard and Ferré, 1982), guinea-pigs (Duée *et al.*, 1983) and breast-fed human babies (Melichar, Drahota and Hahn, 1965 ; Persson and Gentz, 1966 ; Warshaw and Curry, 1980).

In suckling lambs, pigs and dogs (Varnam, Jeacock and Shepherd, 1978 ; Bengtsson *et al.*, 1969 ; Gentz *et al.*, 1970 ; Pégorier *et al.*, 1981 ; Spitzer and Weng, 1972), blood ketone body levels remain very low despite high plasma

NEFA concentrations. The reasons for these species differences are not well understood, but recent experiments on isolated hepatocytes from newborn pigs have shown that 80-85 % of the fatty acids taken up are converted into esterified fats, thus markedly limiting fatty acid oxidation and ketogenesis (Pégorier *et al.*, 1983). However, ketone bodies are unlikely to play a role as energy substrates in the newborn of these species.

b) *Increased plasma glucagon : insulin ratio.* — During the immediate postnatal period there is a marked rise in plasma glucagon and a fall in plasma insulin in rats (Girard *et al.*, 1973 ; Blazquez *et al.*, 1974), rabbits (Callikan *et al.*, 1979), and humans (Sperling *et al.*, 1974). Similar changes occur in both fasted and suckled rat neonates (Girard *et al.*, 1980), and high plasma glucagon and low plasma insulin prevail throughout the suckling period in rats (Blazquez *et al.*, 1972 ; Beaudry, Chiasson and Exton, 1977 ; Girard *et al.*, 1977). These hormonal changes are highly appropriate for the initiation and maintenance of efficient ketogenesis in the liver of newborns.

c) *Intrahepatic regulation of ketogenesis in newborns.* — Most of the information presently available on the development of hepatic ketogenesis has been obtained in rats. *In vitro* studies using liver homogenates (Augenfeld and Fritz, 1970 ; Lee and Fritz, 1971 ; Lockwood and Bailey, 1970 ; Foster and Bailey, 1976b ; Yeh and Zee, 1976, 1979 ; Yeh, Streuli and Zee, 1977 ; Chalk *et al.*, 1983), liver slices (Drahota *et al.*, 1964) and isolated hepatocytes (Ferré *et al.*, 1983) have shown that the rates of long-chain fatty acid oxidation and ketone body production are very low in fetal rat liver and that they markedly increase in newborns from day 1 of age. These changes are accompanied by an increase in the activity of CAT I (Augenfeld and Fritz, 1970 ; Lockwood and Bailey, 1970 ; Warshaw, 1972 ; Foster and Bailey, 1976b ; Yeh and Zee, 1979) and of the enzymes of the hydroxymethyl-glutaryl CoA (HMGCoA) pathway (Lockwood and Bailey, 1971 ; Lee and Fritz, 1971 ; Hipolito-Reis, Bailey and Bartley, 1974 ; Shah and Bailey, 1977). Unfortunately, these studies do not provide any information on the time-course or the possible factors regulating hepatic ketogenesis during the first 24 h of life, the period during which ketogenesis appears in the liver and reaches adult values. Recent experiments using newborn rat hepatocytes, isolated at different times after birth and incubated in the presence of equal concentrations of oleate or octanoate, show that ketogenic capacity increases with both substrates during the 16 h following birth (Girard *et al.*, 1981 ; Ferré *et al.*, 1983). However, octanoate is more ketogenic than oleate (fig. 2). These data confirm that factors other than NEFA availability are responsible for the onset of ketogenesis at birth, and they suggest that CAT I is not the only limiting factor.

Since liver carnitine concentration increases after birth in suckling rats it was suggested that carnitine is a key factor in triggering ketogenesis at birth (Robles-Valdes, McGarry and Foster, 1976). Several lines of evidence indicate that this hypothesis may not be valid : (1) liver carnitine concentration increases 2 h after birth whereas maximal ketonemia is reached only at 12 h after birth (Ferré *et al.*, 1978), (2) 16-hour old starved rats fed with triglyceride emulsion alone or supplemented with carnitine reach the same degree of hyperketonemia (Ferré *et al.*, 1978),

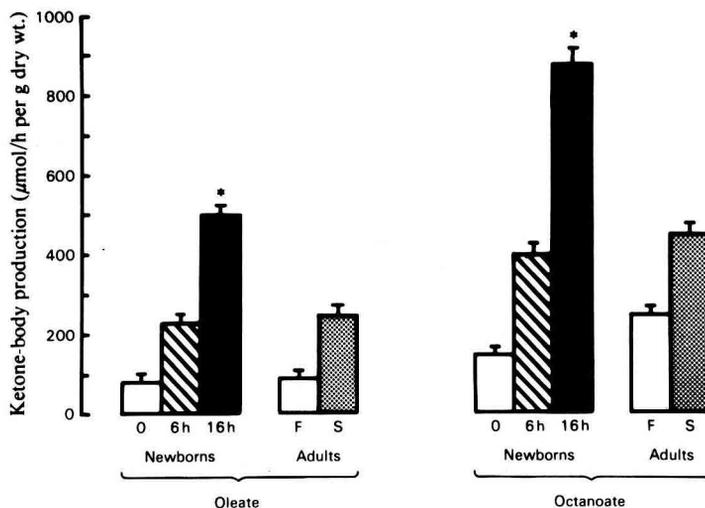


FIG. 2. — Ketogenesis from oleate and octanoate in isolated hepatocytes from newborn and adult rats. Isolated hepatocytes from starved newborn rats and from fed (F) or 48-hour fasted (S) rats were incubated with 0.4 mM oleate or 2 mM octanoate. From Ferré *et al.* (1983).

and (3) ketogenesis from oleate is 6-fold higher at 16 h after birth than at delivery in hepatocytes isolated from newborn rats and incubated with carnitine (1 mM) (Ferré *et al.*, 1983).

Using [1-¹⁴C]-oleate, it has been shown that the increase in ketone body production that occurs between birth and 16 h after delivery does not result from a fall in fatty acid esterification but is related to increased fatty acid oxidation (Ferré *et al.*, 1983).

In adult rats it has been reported that malonyl-CoA, a key intermediate in the lipogenic pathway, inhibits fatty acid oxidation by decreasing the activity of CAT I (McGarry, Mannaerts and Foster, 1977; McGarry, Takabayashi and Foster, 1978). As malonyl-CoA concentrations are directly related to the rate of lipogenesis, this implies that there is an inverse relationship between lipogenesis and ketogenesis. Moreover, in adult rats CAT I sensitivity to malonyl-CoA is decreased in ketogenic states and this might contribute to an increase in fatty acid oxidation (Cook, Otto and Cornell, 1980; Ontko and Johns, 1980; Bremer, 1981; Saggerson and Carpenter, 1981; Cook, Stephens and Harris, 1984). The rate of lipogenesis from ³H₂O is 60 % lower in hepatocytes from newborn rats than in those from fed adult rats, and it decreases to undetectable values in 16-hour old starved newborns (fig. 3; Ferré *et al.*, 1983). In addition, the sensitivity of CAT I to the inhibitory effect of malonyl-CoA decreases between 0 and 24 h after birth (fig. 4; Saggerson and Carpenter, 1982). Thus, it would seem that the onset of ketogenesis at birth could be related to a malonyl-CoA-dependent mechanism. However, the addition of glucagon and 5-tetradecyloxy-2-furoic acid (TOFA, an inhibitor of acetyl-CoA carboxylase) to hepatocytes from newborn rats (0 h) suppresses the rate of lipogenesis by 90 %, but without a simultaneous increase in fatty acid oxidation and ketogenesis

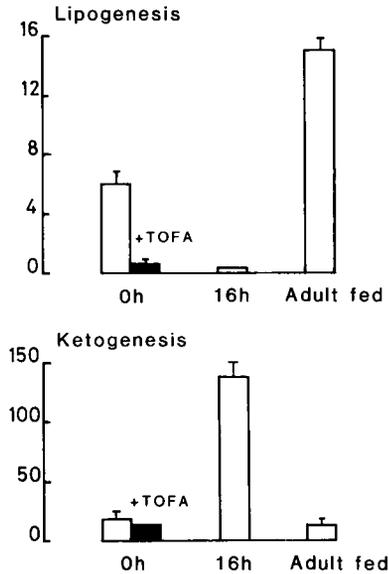


FIG. 3. — *Lipogenesis from $^3\text{H}_2\text{O}$ and ketogenesis from oleate in hepatocytes from newborn and fed adult rats.* Isolated hepatocytes from 0 and 16-hour old starved newborn and fed adult rats were incubated with 0.4 mM oleate, 10 mM lactate and 1 mM TOFA. From Ferré *et al.* (1983).

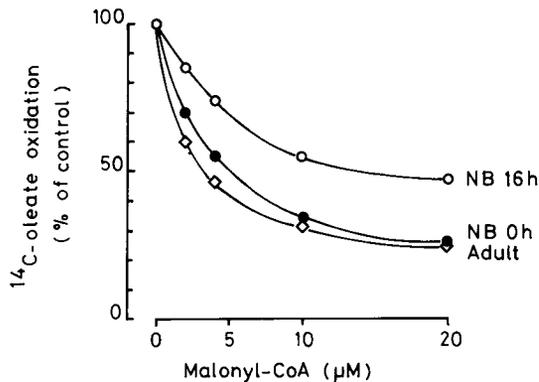


FIG. 4. — *Effect of malonyl-CoA concentration on $[^{14}\text{C}]$ -oleate oxidation by isolated mitochondria from 0 and 16-hour old starved newborn and fed adult rats.* The concentration of malonyl-CoA necessary to inhibit 50 % of the oleate oxidation was : 6 μM in 0-hour old newborns, 14 μM in 16-hour old newborns and 3 μM in adults (Escriva, Decaux, Ferré and Girard, unpublished data).

(fig. 3 ; Ferré *et al.*, 1983). This suggests that malonyl-CoA is not the factor responsible for the switch-on of hepatic fatty acid oxidation and ketogenesis in newborn rats.

In newborn rats, octanoate oxidation is considered to be independent from the step catalysed by CAT I (Ferré *et al.*, 1983). Ketone body production from octanoate increases 6-fold between 0 and 16 h after birth in hepatocytes from starved newborn rats (Ferré *et al.*, 1983), indicating alterations in metabolic

regulation at sites including octanoyl-CoA formation, β -oxidation and the HMGCoA pathway.

The capacity for β -oxidation and ketogenesis in guinea-pigs develops maximally during the first 6-12 h after birth (Shipp, Parameswaran and Arinze, 1982 ; Stanley, Gonzales and Baker, 1983). Studies using liver homogenates (Stanley, Gonzales and Baker, 1983) or isolated mitochondria (Shipp, Parameswaran and Arinze, 1982) suggest that ketone body synthesis in newly-born guinea-pigs is limited by three different factors : (1) the formation of acylcarnitine (CAT I), (2) intramitochondrial capacity for β -oxidation and (3) the activation of medium-chain fatty acids.

2. Suckling-weanling transition.

In the suckling period, rat pups receive milk with a high-fat content and containing a high proportion of medium-chain fatty acids (Jenness, 1974). Physiological hyperketonemia occurs until the pups are weaned on to a commercial high-carbohydrate diet between 18 and 30 days after birth (Drahota *et al.*, 1964 ; Page, Krebs and Williamson, 1971 ; Lockwood and Bailey, 1971 ; Dahlquist, Persson and Persson, 1972 ; Robles-Valdes, McGarry and Foster, 1976). Some of the enzymes concerned in fatty acid oxidation and ketogenesis show high activity during the suckling period but this activity declines to adult values at weaning (Foster and Bailey, 1976a ; Shah and Bailey, 1977). Particularly marked changes occur in CAT I activity which correlate well with the rate of palmitate conversion into ketone bodies by liver mitochondria (Foster and Bailey, 1976b). The rate of ketogenesis from endogenous substrates and from oleate in isolated hepatocytes from fed suckling rats decreases by 50 to 70 % in the immediate post-weaning period (Benito, Whitelaw and Williamson, 1979 ; Decaux *et al.*, 1985), whereas that from butyrate does not alter appreciably over this period (Benito, Whitelaw and Williamson, 1979). Moreover, the rate of hepatic lipogenesis, which is very low during the suckling period (Ballard and Hanson, 1967 ; Taylor, Bailey and Bartley, 1967 ; Lockwood, Bailey and Taylor, 1970 ; Benito, Whitelaw and Williamson, 1979 ; Sly and Walker, 1978), increases at the time of weaning. There is also a reciprocal relationship between ketogenesis and lipogenesis in isolated hepatocytes from weanling rats (Benito, Whitelaw and Williamson, 1979), indicating that, as in adult rats, the major site of ketogenic regulation during this period involves the distribution of long-chain fatty acyl-CoA between the pathways of esterification and β -oxidation. However, inhibiting the high rate of lipogenesis by TOFA in hepatocytes from weanling rats does not alter the rate of ketogenesis (Benito, Whitelaw and Williamson, 1979 ; Decaux *et al.*, 1985). It may be that the mitochondrial capacity to oxidize fatty acids changes during the weaning period (see Decaux *et al.*, 1985).

During this same period, a progressive decrease in plasma glucagon and a significant increase in plasma insulin are observed (Girard *et al.*, 1977 ; Blazquez *et al.*, 1972 ; Beaudry, Chiasson and Exton, 1977) concomitantly with a drop in hepatic ketogenesis and a rise in hepatic lipogenesis. When rats are weaned prematurely to a high-fat diet, after 18 days of age, ketogenesis remains as high as it was during suckling (Decaux *et al.*, 1985), whereas the rise in liver

lipogenesis is prevented (Hahn and Kirby, 1973 ; Bailey and Lockwood, 1973 ; Decaux *et al.*, 1985). In this case, plasma glucagon remains very high and plasma insulin very low (Girard *et al.*, 1977), indicating that the rise in the plasma insulin : glucagon ratio could account for the shift in hepatic metabolism occurring during the weaning period.

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Résumé. *Oxydation des acides gras et cétogénèse au cours du développement.*

Les acides gras sont les substrats oxydatifs principaux du cœur, des muscles squelettiques, du cortex rénal et du foie chez les Mammifères adultes. Ils sont fournis à ces tissus soit sous la forme d'acides gras non-estérifiés soit sous la forme de triglycérides, après hydrolyse par la lipoprotéine lipase.

Pendant la vie fœtale, la capacité de ces différents tissus à oxyder les acides gras est très faible, même dans les espèces où le transfert placentaire d'acides gras et de carnitine s'effectue facilement. A la naissance, la capacité des différents tissus à oxyder les acides gras d'origine endogène ou fournis par les lipides du lait se développe rapidement et reste très élevée pendant la période d'allaitement. La capacité cétogénétique se développe dans le foie 6 à 12 heures après la naissance et les corps cétoniques servent de substrats oxydatifs à de nombreux tissus pendant toute la période de l'allaitement. Au moment du sevrage, le passage d'une alimentation lactée riche en lipides à l'alimentation du rat de laboratoire riche en glucides s'accompagne d'une diminution progressive des capacités cétogénétiques du foie alors que d'autres tissus (cœur, muscles, rein) conservent une capacité élevée d'oxyder les acides gras. Les facteurs nutritionnels et hormonaux impliqués dans les modifications des capacités d'oxydation des acides gras au cours du développement sont discutés dans cet article.

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