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Developmental Aspects of Lipid Metabolism

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Summary

It was confirmed that the main source of energy for growth and development in the neonatal period was fat. Considerable attention was paid to the development of both white adipose tissue (WAT) and brown adipose tissue (BAT) in the rat and human newborn. Cholesterol metabolism during development was studied in the liver, the small intestine and both WAT and BAT. Brown adipose tissue of rats and adipose tissue from human newborns require carnitine for optimum respiration and fatty acid oxidation. Surprisingly, carnitine enhanced lipolysis in human newborn adipose tissue, Intravenously-fed newborn patients exhibited a rapid decrease of plasma level of carnitine and its esters, indicating a greater requirement for exogenous carnitine than in adult subjects (52 references)

Key words

Energy sources – Fat metabolism – Cholesterol metabolism – White and brown adipose tissue – Carnitine synthesis – Carnitine in milk

Lipid metabolism in the perinatal period

It was shown that the main source of energy for growth and development in the neonatal period is fat. This was particularly true for the rat (Hahn and Koldovský 1960, 1961, Hahn *et al.* 1963, 1964a,b, Novák *et al.* 1965a), and though less evident, for the human (Hahn and Koldovský 1966, Novák *et al.* 1965b). In the rat, blood levels of cholesterol, free fatty acids and triglycerides are low at birth and rise rapidly after delivery, falling again at the time of weaning (Grafnetter *et al.* 1960). Similar changes were observed in the human newborn (Hahn 1979, Melichar *et al.* 1962, Novák *et al.* 1961, 1964). Considering that the fat is the main energy source in the infant mammal, it is speculated that this might lead to increased ketone formation. It was found that plasma levels of ketone rise considerably after birth in the rat (Drahota *et al.* 1964). Similar, but less pronounced, increases in blood ketone levels were also found in the human newborn (Hahn and Novák 1975, Hahn 1982, 1985). Ketone production in the foetal rat liver was very low and increased suddenly after birth (Drahota *et al.* 1964). However, the brain of neonatal rats preferentially utilizes ketones as first demonstrated by Drahota *et al.* (1965).

Considerable attention was paid to the development of both white adipose tissue (WAT) and brown adipose tissue (BAT) in the rat and human newborns. This was reviewed in detail by Hahn and Novák (1975). It is also of particular interest that WAT in newborns apparently consists of two types of tissue, one of which behaves like brown fat and contains a large amount of mitochondria and is responsive to carnitine. Brown adipose tissue is the thermogenic organ that effectively participates in the maintenance of thermal homeostasis in newborn mammals and in adult hibernating animals. The high triglyceride content of brown adipose tissue cells, the high oxidative capacity (Houštěk *et al.* 1978), low ATPase activity (Houštěk *et al.* 1978), and specific mitochondrial proton channel (Kopecký *et al.* 1987) which enables energy dissipation in the form of heat which are involved in protection of newborn mammals against cold. Free fatty acids released from cytosolic carnitine-dependent pathways (Drahota *et al.* 1968) and lipids are thus the main fuel for heat production by BAT cells. The thermogenic function of brown adipose tissue cells can be used not only for maintenance of thermal homeostasis of vital organs during the cold stress, but also for the maintenance of energy homeostasis in situations when the mammalian body is overloaded with high energy substrates. Defects of BAT function may be one of the

factors that participate in the development of obesity (Soukup *et al.* 1989).

It was also shown that fatty acid metabolism, as related to triglycerides and phospholipids formation in different tissues in the perinatal period, changes considerably in relation to milk composition (Dobiášová *et al.* 1963, 1966, Dobiášová and Hahn 1968). In BAT, carnitine is essential for the increased heat production which occurs in that tissue.

Cholesterol metabolism during development was studied extensively. The enzyme committing acetoacetyl CoA to cholesterol synthesis, hydroxymethylglutaryl-CoA reductase (HMGR) was examined in detail in the liver, the small intestine and both WAT and BAT (Kroeger and Hahn 1983). It was found to have low activity in sucklings and to rise at weaning. The same is true for 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis (Hahn and Innis 1984). Finally, acyl-CoA cholesterol-acyl transferase (ACAT) activity was also examined during development. This did not follow the pattern of acylcholesterolacyl-CoA transferase (Little and Hahn 1992).

Dobiášová *et al.* (unpublished data) examined the concentration of lipids, the rate of esterification of cholesterol in high density lipoprotein (HDL), and the composition of the HDL subpopulation in 125 children aged 3 months to 16 years. Sixty-one children were in the hospital with common infections and 64 had heart surgery. Gradient gel electrophoresis was used to assess the state of the HDL, together with the functional test for determining the fractional esterification rate (FER). In children below the age of 4 years, the HDL cholesterol concentration and the content of HDL2 were significantly lower as compared to that of older individuals. On the other hand, the HDL-FER was greater in the younger group. No age differences in plasma cholesterol and triglyceride content were found. This study confirmed that the rate of esterification of cholesterol is regulated by HDL2b (negatively) and HDL3b (positively) as it is in adults. A tendency to sex differences in HDL composition and the rate of HDL esterification were present only in the older children. It follows that changes in the composition of the HDL subpopulations, that may be related to the risk of atherosclerosis, occur during postnatal development.

Carnitine

The first paper showing that brown adipose tissue requires carnitine to produce extra heat was published by Drahota *et al.* (1968). Soon after, it was shown that adipose tissue from human newborns also requires carnitine for optimum respiration (Novák *et al.* 1969, 1973) and fatty acid oxidation (Schmidt-Sommerfeld *et al.* 1978).

It was later shown in the rat and mouse that carnitine enhances the rate of oxygen consumption stimulated by norepinephrine (Hahn *et al.* 1971). The carnitine and acetylcarnitine content of BAT rises rapidly to a peak on day 10 in infant rats as does the activity of carnitineacetyl transferase. Exposure of 18-day-old rats to cold again raises the carnitine and enzyme activity. No other tissue (muscle, liver, heart) had such a high carnitine content (Hahn and Skála 1972, 1975). Carnitineacyl transferases were also found in the human foetal liver and heart, but were very low in the muscles (Hahn and Skála 1973). Surprisingly, carnitine also enhanced lipolysis in human newborn adipose tissue (Novák *et al.* 1975). A comparative study of carnitine transferases in BAT of human and monkey foetuses and adults showed higher activity in BAT than in the other tissues examined (Hahn *et al.* 1976). The carnitine content in amniotic fluid and maternal blood was found to be low in humans with higher foetal blood levels than in the mother (Hahn *et al.* 1977, Novák *et al.* 1979, Bargen-Lockner *et al.* 1981).

In both rat and human plasma, carnitine levels depend on the diet (Frohlich *et al.* 1978, Seccombe *et al.* 1978); levels being higher in suckling rats and decrease in adult humans subjected to starvation. In these levels, urinary excretion of carnitine and its esters is enhanced. The first "practical" paper concerning carnitine and the human newborn was published by Schiff *et al.* (1979). Intravenously-fed newborn patients had a rapidly decreased plasma level of carnitine and its esters, indicating a greater requirement for exogenous carnitine than in adult patients (Hahn *et al.* 1982, Hahn and Novák 1985). In adult obese patients, plasma carnitine levels decreased after jejuno-ileal bypass surgery, most likely because food intake was reduced (Frohlich *et al.* 1980, Seccombe *et al.* 1984). The low plasma levels of newborn rats and human infants may be due to either decreased endogenous synthesis or decreased exogenous supply. In the rat, synthesis of carnitine from gamma butyrobetain increases postnatally (Hahn 1981). However, this is not thought to be the rate-limiting step.

On the other hand, milk contains a considerable amount of carnitine. Human milk has about 60 nmoles/ml compared to a zero amount in soy bean based formulae (Novák *et al.* 1979, Novák 1990). Therefore, it seems likely that an exogenous supply of carnitine is of some importance in the neonatal period (Novák 1990, Novák *et al.* 1988). Other studies have demonstrated considerable carnitine content in rat bile (Hamilton and Hahn 1987), and more recent studies suggest that carnitine administration lowers plasma cholesterol levels in hyperlipaemic rabbits (Seccombe *et al.* 1987).

It may thus be concluded that carnitine plays an important role whenever fat is being utilized, i. e. in the early postnatal period, during food deprivation and when a high-fat diet is fed.

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