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Integration of carbohydrate and lipid metabolism in skeletal muscle during postnatal development

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Summary. In the adult, muscle metabolism represents a large drain of energetic substrates. The newborn has to provide additional energy to its muscles in order to ensure a rapid growth. However, since during the neonatal period the newborn is fed with a high-fat low-carbohydrate diet, i.e., milk, the newborn must also spare glucose for organs which are obligatory glucose consumers such as the brain. Thus, regulation of energetic substrate utilisation by muscle is of upmost importance for postnatal metabolic homeostasis.

In the human, fibre types at birth can already be histochemically classified as adult types and the proportional distributions of each fibre-type approximate those seen in the adult. On the other hand, glycolytic and oxidative maximal enzyme activities are lower than adult levels.

In the rat, the capacity for glucose utilisation in muscles is low at birth, reaches a peak at weaning and subsequently decreases. During the suckling period, the concentration of lipid-derived substrates is high as well as the muscle capacity for their oxidation; moreover, insulin concentration is low and insulin sensitivity of muscle glucose utilization is also reduced. Thus, during the suckling period, fuel availability and insulin concentrations, as well as tissue sensitivity towards the hormone, favour the limitation of glucose utilisation by skeletal muscles.

Introduction.

After birth, the neonate must undergo a multitude of physiological adaptations to its extraterrestrial environment. In utero, there is a constant substrate supply which is regulated by parental metabolism. In contrast, the neonate must adapt to intermittent periods of feeding by controlling mobilization and utilization of carbohydrates, lipids and protein to meet demands during post-absorptive periods.

In addition, fuels available to the neonate change dramatically after parturition; in utero, carbohydrate and amino acids have been supplied for anabolic and catabolic needs, whereas the neonate receives a high-lipid diet with a smaller carbohydrate component. Since brain, which in the newborn represents a higher percentage of body mass [the brain of the human neonate represents 12 % of the
body mass compared to 2.5% in the adult (Dobbing & Sands, 1973)], is an obligatory glucose consumer, the newborn has to adapt itself to this new situation. This is achieved in two ways: at first the newborn can activate its endogenous glucose production. It is indeed well established that the gluconeogenic pathway is active after birth in the human (Kalhan, Savin & Adam, 1976; Bier et al., 1977; Denne and Kalhan, 1986) and in other species (Girard and Ferré, 1982); the newborn could spare glucose in tissues able to utilise alternative lipid or lipid-derived substrates. It has been shown for instance that ketone bodies are quantitatively important substrates for the neonatal brain (Settergren, Linblad and Persson, 1976), being used catabolically to reduce the requirement for glucose (Kraus, Schlenker and Schwedesky, 1974; Adam et al., 1975) and anabolically as lipid precursors (Patel et al., 1975). It has been shown in the adult man that after the brain, the muscles, even in the resting state, represent quantitatively the most important mass of tissue for glucose utilisation (De Fronzo et al., 1981).

In other species such as the rat, in which glucose consumption by the brain represents a minor drain on glucose metabolism, muscle can even represent the most important mass of tissue consuming glucose (Ferré et al., 1985). Therefore, regulation of substrate utilisation by muscle is of upmost importance for postnatal metabolic homeostasis.

This review will discuss the integration of carbohydrate and lipid metabolism by muscle in the neonate.

1. Fiber types and biochemical differentiation.

In the human foetus up to the 30th week of gestation, skeletal muscle consists largely of undifferentiated fibres (Tomanek and Colling-Saltin, 1977; Colling-Saltin, 1978a); however, between 31 weeks of gestation and parturition, rapid differentiation of fibres occurs, such that at birth over 80% of the muscle fibres can be histochemically classified (Brooke and Kaiser, 1970) as type I, Ila or IIB, and the proportional distributions of each fibre-type approximate those seen in the adult (Sillau and Banchero, 1977; Colling-Saltin, 1978a). This suggests that post-natal growth of skeletal muscle is mainly due to hypertrophy of existing fibres (Goldspink, 1970).

At birth, muscle glycogen and triacylglycerol content are similar to those seen in the adult muscle (Colling-Saltin, 1978b). On the other hand, glycolytic and oxidative maximal enzyme activities are lower than adult levels; thus, in human skeletal muscle sampled shortly after birth, 6-phosphofructokinase and succinate dehydrogenase activities are 50% and 40% respectively of adult values (Colling-Saltin, 1978b). Similar findings have been reported in animal experiments; a comparison of enzyme activities in heart, diaphragm and quadriceps muscle of adult and newborn rats demonstrates that neonatal muscle contains lower activities of citrate synthase and cytochrome oxidase, the difference between neonatal and adult oxidative capacity being greatest in skeletal muscle (Novak et al., 1972; Baldwin et al., 1978; Glatz and Veerkamp, 1982) and least in cardiac muscle (Baldwin, Cooke and Cheadle, 1977; Glatz and Veerkamp, 1982).
In the immediate postnatal period, protein synthesis is sufficiently active, such that in the rat, rates of protein deposition allow a 10-fold increase in body weight between birth and 30 days of age (Winick and Noble, 1965), more than 60% of protein synthesis occurring in cardiac and skeletal muscle (Miller, 1970). In addition to large increases in structural and contractile protein concentration in muscle, there are also increases in the capacities of the enzymes of carbohydrate metabolism, such that maximal activities of glycolytic and oxidative enzymes approach those measured in the adult by the fourth week of extrauterine development in the human neonate (Colling-Saltin, 1978b). Hypertrophy of muscle fibres causes a decrease in capillary density (Sillau and Banchero, 1977; Ripoll, Sillau and Banchero, 1979) which is partially compensated for by an increase in cellular myoglobin concentration (Wittenberg, 1970; Henquell, Odoroff and Honig, 1976).

2. Carbohydrate metabolism by muscle.

*Development of the capacity for glucose utilization in muscles.* — A number of studies conducted in vitro have investigated whether glucose utilisation by cardiac and skeletal muscle changes during development. The general conclusion of such studies is that the capacity for glucose utilisation decreases with age (Goodman and Ruderman, 1979; Goodman et al., 1983).

The methodology used in these experiments involves in vitro determination of glucose utilisation rates by measuring the accumulation of metabolic end-products (e.g. lactate, CO\(_2\), glycogen) or introduction of a non-metabolizable analogue of glucose (e.g. 2-deoxyglucose, 3-O-methylglucose) in muscle preparations such as the isolated, perfused heart, the perfused hindquarter or incubated, isolated muscle preparations (Goldberg, Martel and Kushmerick, 1975) where glucose is administered as the sole metabolic substrate. Under these conditions, glucose transport is the pseudo-flux-generating step for glucose utilization (Newsholme and Crabtree, 1979). Changes in rates of glucose transport are caused by a change in the distribution of glucose transporter units between the «active» plasma membrane fraction and the «covert» microsomal transporter pool (Wardzala and Jeanrenaud, 1981). Wang (1985) has shown that basal rates of glucose transport are highest in incubated rat diaphragm prepared from animals shortly after birth, subsequently rates of glucose transport decrease by 60-70% over the first 40 days of post-natal development (fig. 1). The total pool size of glucose transporter units (sarcolemmal plus microsomal) also declines by about 60% over a similar time period (Wang, 1985).

Few studies have investigated the capacity for the metabolism of glucose distal to the transport step. Goddman et al. (1983) showed that the rate of glucose uptake by the perfused hindquarter of rats decreased by 60% between 3 and 8 weeks of age (fig. 1); however, the fraction of glucose metabolized to lactate remained constant at about 55%, suggesting no changes in the relative capacities of glycolysis and other metabolic pathways (glycogen synthesis and pyruvate oxidation).
3. Lipid metabolism by muscle.

In mammals, during the suckling period, 50-70% of the caloric intake is in the form of lipids (Ferré et al., 1986). In rats (Page, Krebs and Williamson, 1971; Foster and Bailey, 1976; Robles-Valdes, McGarry and Foster, 1976) as well as in humans (Bougneres et al., 1982, 1986), plasma triacylglycerol, free fatty acids and ketone bodies are elevated in the neonate when compared to post-weaning or adult values.

In addition to increased lipid availability to cardiac and skeletal muscles, the available evidence suggests that the capacity for lipid catabolism is increased in postnatal muscle. Lipoprotein lipase activity in cardiac and skeletal muscle increases markedly at birth (Cryer and Jones, 1978), enhancing the local concentration gradient of free fatty acids at the sarcolemma. The capacity of heart (Wittels and Bressler; 1965; Warshaw, 1972; Mersmann and Phinney, 1973; Aprille, 1976; Wolfe, Maxwell and Nelson, 1978; Werner et al., 1982, 1983) and skeletal muscle (Wolfe, Maxwell and Nelson, 1978; Glatz and Veerkamp, 1982; Caroll et al., 1983) to oxidize non-esterified fatty acids increases shortly after birth in rats, rabbits and calves. This change is paralleled by an increase in the number of mitochondria and in the activities of enzymes associated with oxidative
metabolism of non-esterified fatty acids and specially of carnitine acyl transferase which catalyzes the mitochondrial entry of long chain fatty acyl-CoA (Wittels and Bressler, 1965; Warshaw 1972, 1974; Barrie and Harris, 1977; Glatz and Veerkamp, 1982); the increase in carnitine acyl transferase is concomittant of an increase in the tissue concentrations of carnitine (Robles-Valdes et al., 1976; Borum, 1978; Caroll et al., 1973), an essential cofactor for the enzyme (Frenkel and McGarry, 1980a). After weaning, the oxidative capacity remains high in heart (Warshaw, 1972; Glatz and Veerkamp, 1982; Werner et al., 1982) and, to a lesser extent, in skeletal muscles.

Ketone body utilisation is regulated by the blood substrate concentration and by the metabolising capacity of tissues. Whereas the capacity of the neonatal brain to utilise ketone bodies increases after birth and is higher during the postnatal period than in adult brain, the activity of specific utilising enzymes is lower in other tissues and specially in the heart (Williamson, 1982). These data suggest that in the newborn, ketone bodies could be preferentially channeled towards the brain.

4. Integration of carbohydrate and lipid metabolism in muscle.

4.1. The glucose/fatty acid cycle in adults. — The concept of a glucose/fatty acid cycle was proposed by Randle and coworkers to explain the reciprocal relationship between the rates of oxidation of glucose and fatty acids by muscle (Randle et al., 1963). Subsequently, this concept was extended to encompass ketone body metabolism (Newsholme, 1976). Fatty acids and ketone bodies can inhibit glycolysis and glucose oxidation (Newsholme, Randle & Manchester, 1962; Randle, Newsholme & Garland, 1964); provision of acetyl-CoA from β-oxidation of fatty acids or catabolism of ketone bodies causes an increase in mitochondrial acetyl-CoA/CoASH and NAD/NADH ratios which inhibits pyruvate dehydrogenase activity and increases phosphorylation and inactivation of pyruvate dehydrogenase (Randle et al., 1978). Furthermore, increased oxidation of ketogenic fuels causes an increase in cellular citrate concentration which potentiates ATP inhibition of 6-phosphofructokinase, inhibiting glycolysis and causing an increase in hexose-monophosphate concentration; this, in turn, inhibits glucose phosphorylation by hexokinase and may increase glycogen synthesis by allosteric activation of glycogen synthase (see Randle, 1981 for review).

Lipid-derived substrate oxidation affects glucose utilisation in adult mammalian cardiac muscle (Newsholme, Randle & Manchester, 1962; Randle, Newsholme & Garland, 1964; Kauppinen, Hiltunen & Hassinen, 1982); its operation and quantitative importance in overall glucose homeostasis in skeletal muscle in vivo is more controversial (Ruderman et al., 1980; Zorzano et al., 1985) although it has been demonstrated recently that a 48 h-fast induced a 80% decrease of glucose utilisation in oxidative muscle in awake rats (Issad et al., 1987a).

4.2. Decreased glucose oxidation induced by lipid-derived substrates. — In neonatal skeletal muscle, it is likely that the increased availability of fatty acids and ketone bodies and the enhanced capacities of the pathways of fatty acid and
ketone body utilization cause increases in acetyl-CoA/CoASH and NADH/NAD ratios and inhibition of pyruvate oxidation. Although no direct evidence for an operative muscle glucose/fatty acid/ketone body cycle is available, it has been shown in the suckling newborn rat that lipid oxidation decreases glucose oxidation by inactivating pyruvate dehydrogenase (Pégorier et al., 1978, 1983) and thus increases lactate production from glucose. A similar mechanism has been postulated in the human newborn oxidizing ketone bodies (Bougnères et al., 1983). In studies using [1-13C] glucose infusion and indirect calorimetry to assess glucose metabolism in the 2 day-old human neonate fasted for 4-8 h, Denne and Kahlan (1986) found that the glucose oxidation rate was 2.67 ± 0.34 mg·Kg⁻¹·min⁻¹ and glucose recycling occurred at a rate of of 1.87 ± 0.74 mg·Kg⁻¹·min⁻¹, suggesting a significant production of lactate, with skeletal muscle potentially making the most important contribution.

4.3. Decreased glucose uptake induced by lipid-derived substrates. — Theoretically, glycolysis and thus glucose uptake could be inhibited in neonatal muscle as demonstrated in adult muscle. In newborn rats compared at similar blood glucose concentrations, the availability of lipid-derived substrates decreases overall glucose utilization by 30% (Ferré, Turlan & Girard, 1985). Since muscles represent an appreciable part of the tissues metabolizing glucose, it is likely that they are involved in this phenomenon.

When measuring in vivo the basal rate of glucose utilization by using the 2-deoxyglucose technique (Ferré et al., 1985), it can be shown that this utilization is lower in soleus muscle, diaphragm and heart when compared to weaned or adult animals (Issad, Coupé, Pastor-Anglada, Ferré & Girard, unpublished results).

Clearly, further work is necessary to assess the quantitative significance of the glucose-fatty acid cycle in muscle and its contribution to glucose homeostasis in the neonatal period, specially in the human species.

5. Hormonal regulation of muscle metabolism.

Many hormones interact with specific receptors in skeletal muscle including insulin, catecholamines, glucocorticoids and thyroid hormones. Our understanding of how these hormones might regulate and coordinate metabolism in the neonate is again largely drawn by extrapolation from studies performed in adult animals. On the other hand, plasma hormone profiles for animals during the period from late gestation through the postnatal period are available (Girard et al., 1977; Kaplan, 1981; Sperling, 1983; Katz, Boland & Schmidt, 1985; Abuid, Stinson & Larson, 1973).

At birth, plasma catecholamines increase acutely causing substrate mobilization through hepatic and muscle glycogenolysis and adipose tissue lipolysis, ensuring a ready substrate supply post-partum until suckling begins (Girard & Ferré, 1982). The glucagon/insulin ratio remains high throughout the suckling period and an active gluconeogenesis and ketogenesis are maintained (Girard et
Circulating peripheral insulin concentrations are similar to those seen in fasting adult animals, increasing towards adult levels at weaning (Girard et al., 1977).

Thus, fuel availability and hormone balance in the blood favour the limitation of glucose utilization by skeletal muscle, despite the normal or elevated capacity of neonatal muscle for glucose transport determined in vitro (Goodman et al., 1983; Wang, 1985).

Furthermore, the sensitivity and responsiveness of skeletal muscle to insulin may change during development. Recent studies by Issad et al. (1987b) have shown that higher concentrations of plasma insulin are required to suppress rates of hepatic glucose production and stimulate peripheral glucose utilization, suggesting that an insulin-resistant state exists in the suckling rat which disappears after weaning; on the other hand, Wang (1985, 1986) (fig. 1) has shown that insulin-stimulated glucose transport in rat diaphragm was low at birth and reached a maximum around the weaning period. This phenomenon was not related to a decrease in the intracellular pool of glucose transporter nor to a decrease in the tyrosine kinase activity of the insulin receptor, suggesting that during the suckling period an intrinsic defect in translocation of glucose transporters exists.

In vitro studies (fig. 1) (Goodman et al., 1983; Wang, 1985), as well as the comparison of in vivo effects of insulin on glucose utilization in various muscles in weaned or adult rats (Pénicaud et al., 1987), suggest that insulin sensitivity and responsiveness decrease with age between weaning and adulthood.

In summary, insulin effect on glucose utilization by muscles is low at birth, reaches a peak at weaning and then decreases with age. The underlying mechanisms are still poorly understood.

Résumé. Métabolisme glucidique et lipidique dans le muscle au cours du développement.

La masse musculaire est un organe quantitativement important en ce qui concerne l'utilisation des substrats énergétiques glucidiques et lipidiques.

Le nouveau-né doit fournir de fortes quantités d'énergie à ses muscles afin d'assurer une croissance rapide. Cependant, pendant la période néonatale, le nouveau-né est nourri avec un régime riche en lipides et pauvre en glucides, le lait. Il doit donc également épargner du glucose pour les organes tel que le cerveau qui sont des utilisateurs obligatoires de ce substrat. La régulation du métabolisme énergétique dans les muscles revêt donc une extrême importance pour l'homéostasie métabolique postnatale.

Chez l'homme, on peut à la naissance classer les fibres musculaires d'un point de vue histochemique en catégories semblables à celles observées chez l'adulte. Leurs proportions respectives sont d'ailleurs assez semblables chez le nouveau-né et chez l'adulte. Cependant, les activités maximales des enzymes de la glycolyse et du métabolisme oxydatif sont plus faibles que chez l'adulte.

Chez le rat, la capacité des muscles à utiliser le glucose est faible à la naissance, maximale au moment du sevrage puis diminue avec l'âge. Pendant la période d'allaitement, les concentrations circulantes des substrats énergétiques dérivés des lipides sont élevées.
de même que les capacités musculaires pour leur oxidation ; de plus, la concentration plasmatique d'insuline est faible pendant l'allaitement et la sensibilité à l'insuline réduite. Tous ces facteurs concourent à limiter l'utilisation de glucose dans les muscles pendant la période néonatale.

References


