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Uptake of beta-hydroxybutyrate, acetoacetate and glucose by the forearm of the newborn infant

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Forearm muscle metabolism was studied in twelve appropriate for gestational age premature infants suffering from respiratory distress. Arterial blood was obtained by puncture of the radial artery as clinically indicated for measuring oxygen tension, and venous blood samples were taken from the same arm's deep brachial vein. This arrangement allowed to study the arterial–deep venous differences of beta-hydroxybutyrate, acetoacetate and glucose in simultaneously taken blood samples. Net muscular uptakes of beta-hydroxybutyrate and glucose were observed, however, in four studies a virtual net production of acetoacetate was found. The arterial–deep venous concentration differences of both ketone bodies correlated positively with their arterial concentration within the 20 to 120 nanomol/ml range. Such a correlation was not observed in glucose utilization. It is concluded that forearm muscles in the neonate take up ketone bodies and this is in part concentration regulated.

Ketone body production is usually regarded as an exclusively hepatic process, ketone bodies being continuously produced by the liver and utilized by extrahepatic tissues [7, 11, 22]. The enzymatic possibilities of utilizing ketone bodies are common among animal and human tissues [3, 6, 8, 9]. The enzyme responsible for the NADH linked reversible reduction of acetoacetate to beta-hydroxybutyrate (beta-hydroxybutyrate dehydrogenase, E.C. 1.1.1.30.) is present in most tissues, tightly bound to the mitochondria [6]. In contrast to the adult organism, the fetal liver apparently behaves like extrahepatic tissues in the fetus because it can oxidize ketones [17].

Fetal tissues have been shown to utilize ketone bodies as oxidative fuels, thereby sparing glucose, and in brain and liver, rates of ketone oxidation are proportional to their concentration [1, 5, 18]. Studies of ketone body utilization by skeletal muscle in man have involved measurements of arteriovenous differences across the forearm or leg [2, 4, 21]. In obese humans starved for three days the ketone body uptake by the forearm muscle represents 50% of the oxygen uptake [12], thus ketone bodies may be an important substrate for skeletal muscle during caloric deprivation.

In contrast to the large number of experiments on adults and animals, little information is available on the ketone body utilizing capacity in neonatal muscle [15]. The aim of the pres-

ent work was to study the uptake of ketones and glucose in the neonatal forearm.

Materials and Methods

Twelve appropriate for gestational age premature infants admitted to the perinatal intensive care unit because of respiratory distress were selected for the study. All infants were considered to be without major medical problems and were in stable clinical condition. Mean birth weight was 1748 g (range, 1430 to 2100 g), each infant was in the first ten hours of life. Following the first clinical examination, a butterfly needle (Minifly, Alois Duschek GmbH, Vienna, Austria) was inserted as deeply as possible into a profound brachial vein for giving parenteral fluid and taking venous blood samples. Arterial blood was obtained by puncture of the radial artery for monitoring oxygen tension and acid-base parameters. Approximately 0.5 ml from the simultaneously collected blood was separated into heparinized test tubes, immediately centrifuged, and the plasma was stored at −20 °C until analysis.

Plasma beta-hydroxybutyrate and acetoacetate level was measured by standard enzymatic methods [10, 23], glucose was estimated by commercially available combined enzymatic kits (Boehringer, Mannheim, FRG). The equations of regression lines were calculated by the least squares method.

Results

A total of twelve studies was performed on ketone body and glucose concentrations. The study comprised results from eleven observations on beta-hydroxybutyrate and eight on acetoacetate. In one instance despite of the high arterial level of beta-hydroxybutyrate (744.63 nanomol/ml) the arterio-venous difference remained unexpectedly low (10.15 nanomol/ml). Four paired blood samples showed a net acetoacetate production, these data were excluded from statistical analysis.

The relationship between arterial beta-hydroxybutyrate concentrations and arterial-venous differences are shown in Fig. 1. There was a close linear correlation ($r = 0.556$) between the arterial beta-hydroxybutyrate supply and uptake in the 20 to 120 nanomol/ml range. The equation of regression line was $y = 0.2429 \times$

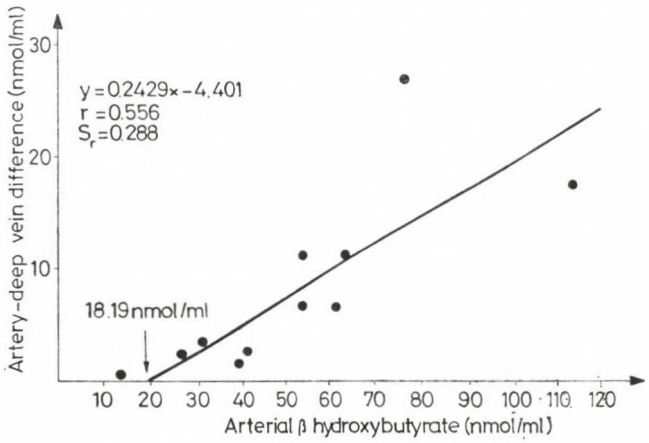

Fig. 1. Arterial concentration of beta-hydroxybutyrate versus its arteriovenous difference (n = 11)

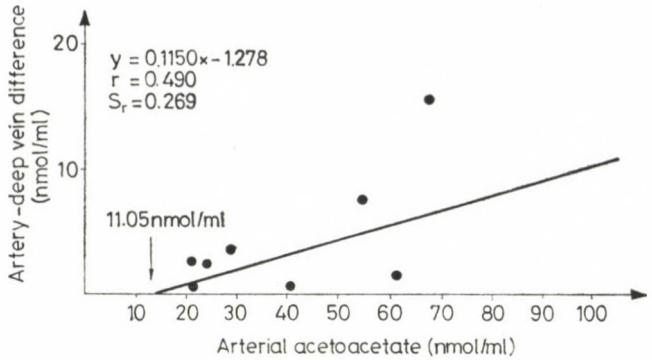

FIG. 2. Arterial concentration of acetoacetate versus its arteriovenous difference in neonatal forearm (n = 8)

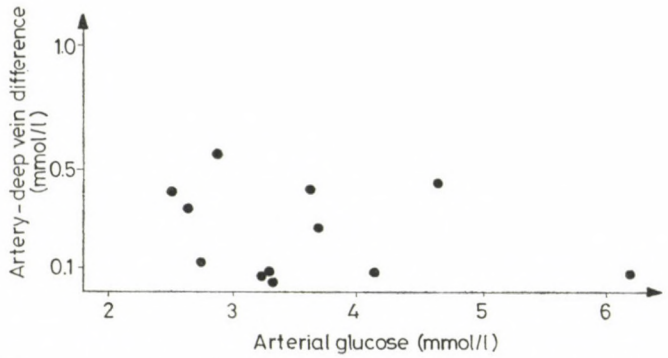

FIG. 3. Arterial concentration of glucose versus its arteriovenous difference (n = 12)

× —4.401. Results of eight observations on acetoacetate uptake by neonatal forearm are shown in Fig. 2. As it is seen, there was a linear correlation between the arterial availability and uptake, the correlation was less striking than in the case of beta-hydroxybutyrate (r = 0.490; the equation was y = 0.115X—1.278). The arterial glucose concentration had no effect on the arterial–deep venous difference, as it is shown in Fig. 3.

DISCUSSION

Due to their low concentration in neonates under normal conditions, beta-hydroxybutyrate and acetoacetate are not major substrates for energy production. Caloric deprivation in neonates and older children is, however, associated with higher ketone levels providing a considerable amount of alternative fuels for metabolism of tissues[19]. In the present study comparatively low beta-

hydroxybutyrate and acetoacetate concentrations were found in the newborns, probably due to the depressed activity of the enzyme carnitine palmitoyl acyltransferase within the first three days of life which makes the neonate unable to produce ketone levels as high as are found in older children [19, 20].

The uptake of both ketone bodies in the present study was found to be a concentration dependent process, the correlation between the arterial ketone levels and the arterial–venous difference was more close in the case of beta-hydroxybutyrate. Similar results were reported on cerebral uptake in adult humans [4, 14]. It seems of interest that in one newborn infant, despite the high arterial beta-hydroxybutyrate level, its uptake from the blood circulation was moderate, suggesting the possibility that its elimination from the blood is saturable at high concentrations.

It is noteworthy that in four studies a virtual net acetoacetate production was observed. In view of this finding the synthetic pathways of acetoacetate should be considered. One possible mechanism is the NAD—NADH interconversion linked reduction of beta-hydroxybutyrate, which reaction depends on the mitochondrial NAD/NADH ratio [6, 15]. This way may represent a "shuttle" function of the ketone bodies in respect of the movement of the reducing equivalents between different tissues and organs depending on their mitochondrial redox state. Another theoretical mechanism of acetoacetate production might be the "de novo" synthesis, for example from free fatty acids, as it has been proposed on the basis of forearm studies in adults [4].

Glucose uptake in the present study was not concentration regulated; corresponding to present knowledge, glucose uptake of skeletal muscle is strongly insulin dependent [13, 16].

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