Journal of Neuroscience Research 79:2–10 (2005)

Mini-Review

Lactate Utilization by Brain Cells and its Role in CNS Development

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We studied the role played by lactate as an important substrate for the brain during the perinatal period. Under these circumstances, lactate is the main substrate for brain development and is used as a source of energy and carbon skeletons. In fact, lactate is used actively by brain cells in culture. Neurons, astrocytes, and oligodendrocytes use lactate as a preferential substrate for both energy purposes and as precursor of lipids. Astrocytes use lactate and other metabolic substrates for the synthesis of oleic acid, a new neurotrophic factor. Oligodendrocytes mainly use lactate as precursor of lipids, presumably those used to synthesize myelin. Neurons use lactate as a source of energy and as precursor of lipids. During the perinatal period, neurons may use blood lactate directly to meet the need for the energy and carbon skeletons required for proliferation and differentiation. During adult life, however, the lactate used by neurons may come from astrocytes, in which lactate is the final product of glycogen breakdown. It may be concluded that lactate plays an important role in brain development.

Key words: lactic acid; neurons; astrocytes; oligodendrocytes; oleic acid

Although the metabolism of lactate by the brain is now a hot issue (Pellerin, 2003; Gladden, 2004), early work showed evidence supporting the crucial role played by lactate in brain metabolism. In fact, lactate is used by the brain in fetal (Bolaños and Medina, 1993), early newborn (Arizmendi and Medina, 1983; Fernández and Medina, 1986; Vicario et al., 1991; Vicario and Medina, 1992), and suckling rats (Itoh and Quastel, 1970; Dombrowski et al., 1989), in adult rat hippocampus (Schurr et al., 1988), in newborn dogs (Hellmann et al., 1982), and in glucose-6-phosphatase-deficient human infants (Fernandes et al., 1984). Lactate utilization by the brain during postnatal period is particularly relevant because in some species such as human, brain develops during this period. This requires a continuous supply of metabolic substrates around birth to maintain brain development. Striking changes in the fuel supply to the tissues occur during the perinatal period because the transplacental supply of nutrients ends with a period of postnatal starvation (presuckling period) followed by adaptation to a fat-rich diet. The aim of the present work is to stress the role played by lactate as a metabolic substrate for the brain during development.

ENERGY HOMEOSTASIS OF THE BRAIN DURING THE PERINATAL PERIOD

The supply of fuels to fetal tissues during gestation is accomplished by transplacental passage of nutrients from the mother, which are mostly glucose, amino acids, and fatty acids. This placental mechanism of transport provides fetal tissues with all the necessary fuels and cofactors to support fetal development. In addition to glucose and amino acids, fetal tissues can be also supplied with lactate, which is an important substrate for the fetal brain during late gestation (Shambaugh et al., 1977). Lactate is transported from the mother to the fetus through placental membranes. In fact, the carrier-mediated transport of lactate occurs in both maternal-sided (Balkovetz et al., 1988; Alonso de la Torre et al., 1991a) and fetal-sided (Alonso de la Torre et al., 1991b) syncytiotrophoblast membranes. The main source of fetal lactate is the placenta itself, however, because the synthesis of lactate from glucose is very high in this tissue during late gestation. Alternatively, fetal tissues may also synthesize lactate owing to the high activity of anaerobic glycolysis in the fetus (Burd et al., 1975; Battaglia, 1989). As a result, lactate accumulates in fetal blood during late gestation (Girard et al., 1977).

Brain development cannot be interrupted despite its restricted fuel supply. Indeed, maternal starvation in the rat decreases the rate of lipogenesis in maternal and fetal

Contract grant sponsor: CICYT; Contract grant sponsor: MEC; Contract grant sponsor: MCYT; Contract grant sponsor: FISSS; Contract grant sponsor: Fundación Ramón Areces, Spain.

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Received 19 July 2004; Revised 7 September 2004; Revised 9 September 2004

Published online 30 November 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jnr.20336

tissues except fetal brain, in which the rate of lipid synthesis remains unchanged (Lorenzo et al., 1982). Maternal starvation increases ketone body concentrations in fetal and maternal blood (Girard et al., 1977), suggesting that in these circumstances ketone bodies may replace glucose as the main metabolic substrate (Shambaugh et al., 1977). In agreement with this suggestion, maternal starvation increases the activity of the monocarboxylate transporter of placental syncytiotrophoblast membrane that is responsible for the transport of lactate and ketone bodies (Alonso de la Torre et al., 1992). This may be a mechanism to preserve brain development under circumstances in which the glucose supply is diminished. In this context, monocarboxylate transporters are present in fetal brain at midgestation and their expression sharply increases during late fetal and neonatal period (Baud et al., 2003; Fayol et al., 2004), suggesting that the perinatal brain is able to take up lactate efficiently. This is in agreement with early observation that lactate transport to the brain in vivo is very active during the perinatal period (Cremer, 1982).

Immediately after birth, the levels of insulin decrease, coinciding with an abrupt increase in glucagon concentrations (Blázquez et al., 1974; Martín et al., 1981; Mayor and Cuezva, 1985; Girard, 1990). The fall in the insulin/glucagon ratio elicits glycogenolysis and gluconeogenesis in the liver through the enhancement of cAMP concentrations. The surge of cAMP concentrations that follows the decrease in the insulin/glucagon ratio is responsible for the increase in the activities of liver glycogen phosphorylase and phosphoenolpyruvate carboxykinase (Mayor and Cuezva, 1985). Consequently, hormonal changes occurring around birth are responsible for the induction of metabolic processes necessary for the newborn to adapt to the new nutritional state in which glucose is scarce. Despite this, the newborn undergoes profound hypoglycemia during the immediate postnatal period (Shelley and Neligan, 1966; Exton, 1972; Martín et al., 1981; Mayor and Cuezva, 1985; Girard, 1990). Both human and rat newborns show very low blood glucose concentrations throughout the first day of extrauterine life (Persson and Tunell, 1971; Juanes et al., 1986). In the rat, there is a tendency after 2 hr to regain normoglycemia, probably due to the stimulation of liver glycogenolysis and the progressive induction of gluconeogenesis (Mayor and Cuezva, 1985; Girard, 1990). This hypoglycemic period is longer in humans, probably because of the delay in gluconeogenesis induction observed in this species (Bougneres, 1987). It is surprising that the delay in glycogenolysis onset apparently enhances vulnerability of the newborn. Lactate availability during this period may supply energy to neonatal tissues, however, reserving glucose for specific metabolic purposes.

Ketone bodies are a major fuel for the brain during the suckling period and hence the stimulation of ketogenesis at birth is an important metabolic event in adaptation of the newborn to extrauterine life. Ketogenesis is active during late gestation in human fetal liver and the activity of ketogenic enzymes sharply increases immediately after birth in the rat (Hahn and Novak, 1985; Bougneres et al., 1986). In addition to modulation of enzyme activities, the control of ketogenesis also depends on the availability of fatty acids. The increase in fatty acid concentrations that occurs after delivery is due to breakdown of triacylglycerol in white adipose tissue present in human newborns at birth. In the rat, however, plasma fatty acids mostly come from hydrolysis of triacylglycerols from the mother's milk because of the lack of white adipose tissue at birth. Nevertheless, in both species, once lactation is active fatty acids come from the intestinal hydrolysis of milk triacylglycerols, which may be absorbed directly without passage through the lymph (Aw and Grigor, 1980).

The increase in the activities of ketogenic enzymes together with the increase in the availability of fatty acids occurring immediately after delivery result in enhancement of ketogenic capacity of the liver (Girard,1990). This is responsible for the increase in ketone body concentrations observed postnatally. In fact, plasma ketone body concentrations are the main factor controlling the rate of ketone body utilization by neonatal tissues (Robinson and Williamson, 1980). In addition, activities of enzymes involved in ketone body utilization either increase during the first days of extrauterine life, as in the rat (Page et al., 1971), or are already induced during early gestation, as in the human brain (Patel et al., 1975). Moreover, newborn rat brain contains acetoacetyl-CoA synthetase, a unique enzyme that allows an important portion of carbon atoms from ketone bodies to be incorporated into lipid via a highly efficient cytosolic pathway (Williamson and Buckley, 1973). Indeed, there is a strong correlation between lipid synthesis and the activity of this enzyme during brain development (Yeh and Sheehan, 1985). Moreover, ketone body transport across the blood–brain barrier using the monocarboxylate carrier is maximal during the suckling period, in keeping with the idea that ketone bodies play an important role in brain development (Cremer, 1982; Conn et al., 1983).

Ketone bodies are utilized by the newborn brain as a source of energy and carbon skeletons and are incorporated into fatty acids, sterols, acetylcholine, and amino acids (Robinson and Williamson, 1980; Bougneres et al., 1986). Ketone bodies, however, seem to be the major source of carbon skeletons for sterol synthesis during brain development and play a decisive role in the synthesis of brain structures during myelinogenesis (Robinson and Williamson, 1980; Miziorko et al., 1990). Ketone bodies are utilized evenly by neurons, astrocytes, and oligodendrocytes (Edmond et al., 1987; Lopes-Cardozo et al., 1989; Poduslo and Miller, 1991), indicating that they are ubiquitous substrates for brain cells. Acetoacetyl-CoA synthetase activity, however, is higher in oligodendrocytes than in neurons or astrocytes, confirming the special role of oligodendrocytes in myelinogenesis (Pleasure et al., 1979; Lopes-Cardozo et al., 1989; Poduslo and Miller, 1991).

LACTATE AS METABOLIC SUBSTRATE FOR BRAIN DEVELOPMENT

Although the supply of metabolic substrates is maintained mostly during the perinatal period, there is an apparent lack of mobilization of energy reserves immediately after delivery; i.e., during the presuckling period. During this period, the maternal supply of glucose has ceased and alternative substrates have not yet been released. In the rat, fatty acids come exclusively from the mother's milk because of the lack of white adipose tissue at birth. Consequently, free fatty acids are not available in the rat before the onset of suckling (Mayor and Cuezva, 1985; Girard, 1990). In the case of human newborns, however, fatty acid mobilization occurs immediately after birth, although the onset of ketogenesis is delayed, probably as a consequence of a limited supply of carnitine, which is provided mainly by the milk (Hahn and Novak, 1985; Schmidt-Sommerfeld and Penn, 1990). In addition, glycogenolysis and gluconeogenesis are not active immediately after birth, resulting in very low concentrations of plasma glucose (Mayor and Cuezva, 1985; Girard, 1990). In these circumstances, lactate may play an important role as an alternative substrate. In fact, lactate accumulates in fetal blood during the perinatal period and is removed rapidly immediately after delivery (Persson and Tunell, 1971; Juanes et al., 1986).

During the transition to extrauterine life, fetal mitochondria undergo striking changes to enable them to fulfill the functional requirements of an oxygen-rich environment. Rat liver mitochondria thus increase their respiratory efficiency within the first hours after delivery, achieving full ability to use oxygen as a terminal acceptor of electrons. This increases the efficiency of their metabolic machinery to produce energy. The signal triggering the enhancement of mitochondrial respiratory efficiency may be the increase in oxygen availability because adenine nucleotide accumulation by mitochondria apparently plays an important role in the postnatal mitochondria setup (Pollak, 1975; Aprille and Asimakis, 1980; Cuezva et al., 1990). The increase in the synthesis of respiratory complexes, however, together with the enhancement of F1-ATPase synthesis may be the final event responsible for the postnatal increase in rat liver mitochondrial efficiency (Valcarce et al., 1988; Cuezva et al., 1990). Consequently, the increase in oxygen availability due to the onset of ventilation is followed by striking changes in mitochondrial function, which increases the metabolic efficiency. Oxygen concentrations are very low in the fetus although the rate of oxidative metabolism in fetal tissues is detectable, suggesting that oxygen is exchanged rapidly between maternal and fetal blood. Despite this, the rate of oxygen utilization by the fetus is moderate compared to that of the newborn during early neonatal life (Battaglia and Meschia, 1978; Girard and Ferré 1982). Blood oxygen concentrations thus rise sharply immediately after delivery (Harris et al., 1986; Juanes et al., 1986), concurrent with the enhancement of lactate and amino acid oxidation (Medina et al., 1990; Vicario et al., 1990). Moreover, the increase in oxygen availability may trigger the utilization of lactate (Medina et al., 1990), thereby initiating postnatal energy homeostasis.

Actually, lactate accumulated during late gestation is mostly removed within the first hours of extrauterine life (Persson and Tunell, 1971; Medina et al., 1990), indicating that neonatal tissues actively utilize blood lactate. Because gluconeogenesis is not yet induced in these circumstances (Medina et al., 1980; Fernández et al., 1983), lactate is utilized directly as a source of energy and carbon skeletons for neonatal tissues (Medina et al., 1990). Lactate metabolism is particularly relevant in the brain, in which lactate is preferred over glucose, glutamine, or ketone bodies (Arizmendi and Medina, 1983; Fernández and Medina, 1986; Vicario et al., 1991). In addition, lactate is utilized by the neonatal brain not only as a source of energy but also as an excellent precursor of sterols and phospholipids (Vicario and Medina, 1992). Consequently, lactate is the main metabolic substrate for the brain during the presuckling period. This provides a continuous supply of metabolic fuels between delivery and the onset of suckling. It should be mentioned that lactate transport across the blood–brain barrier is maximal in the immature brain as compared to that of adults (Cremer, 1982; Conn et al., 1983; Pellerin et al., 1998a; Fayol et al., 2004). In addition, hypoglycemia increases the rate of entry of lactate into the brain, supporting the importance of lactate as a cerebral substrate during the postnatal period (Hellmann et al., 1982; Medina et al., 1990). Lactate inhibits glucose utilization (Fernández and Medina, 1986; Vicario and Medina, 1992), suggesting that during the presuckling period it is utilized as the main fuel, reserving glucose for specific destinations such as oxidation by the pentose phosphate pathway or glycerogenesis. Lactate utilization, however, is presumably not inhibited by ketone bodies because the presence of 3-hydroxybutyrate at physiologic concentrations does not affect lactate metabolism (Vicario and Medina, 1992). Once the onset of suckling takes place, however, ketone bodies become the major fuel for brain development. Under these circumstances, lactate would be used as the major gluconeogenic substrate (Fernández and Medina, 1986; Medina et al., 1990).

LACTATE UTILIZATION BY NEURONS AND ASTROCYTES

Because neonatal brain actively uses lactate, we decided to investigate lactate metabolism in cultured brain cells. When the rates of lactate utilization were measured in neurons and astrocytes from primary culture under optimal conditions and compared to those of other important metabolic substrates for the neonatal brain (Vicario et al., 1993), it was observed that in both neurons and astrocytes the rate of lactate utilization was higher than that of glucose, 3-hydroxybutyrate, or glutamine. Lactate utilization by neurons and astrocytes has been confirmed widely later by nuclear magnetic resonance (NMR) spectroscopy (Alves et al., 1995; Waagepetersen et al., 1998; Qu et al., 2000; Bouzier-Sore et al., 2003; Tyson et al., 2003). Despite the high rate of lactate utilization shown by

astrocytes in vitro (Vicario et al., 1993), later findings (Bouzier-Sore et al., 2003; Itoh et al., 2003) suggest that in physiologic circumstances neurons preferentially use lactate rather than glucose to support oxidative metabolism whereas astrocytes use glycolysis to supply neurons with lactate.

It is noteworthy that lactate was utilized by both neurons and astrocytes not only as a source of energy but also as a precursor of lipids (Vicario et al., 1993). Lactate was thus incorporated preferentially into saponifiable fractions in astrocytes (Tabernero et al., 1993), but sterol synthesis was also relevant in neurons. In both types of cells, the main phospholipid synthesized from lactate was phosphatidylcholine and the main sterols synthesized were lanosterol in neurons and desmosterol in astrocytes (Tabernero et al., 1993). This is in agreement with the lipid composition of the neonatal brain and confirms the physiologic role played by lactate in brain development.

LACTATE AS AN EXCHANGE SUBSTRATE BETWEEN ASTROCYTES AND NEURONS

Although glucose-6-phosphatase activity has been detected in some astrocytes (Bell et al., 1993), it is accepted commonly that the activity of glucose-6-phosphatase is negligible in astrocytes (Gotoh et al., 2000). This enzyme catalyzes the last step in the pathway of glycogen breakdown and hence glucose-6-phosphate, not glucose, is the end product of glycogenolysis in astrocytes. Accordingly, the products of glycogen breakdown cannot leave the astrocyte because the plasma membrane is not permeable to phosphorylated compounds. This system may serve to confine glucose in the astrocyte end feet surrounding capillaries, preventing its return to the blood. Glucose-6-phosphate may cross gap junctions, however, reaching adjacent astrocytes when it would be transformed into lactate by glycolysis. Nevertheless, in the absence of glycogenolysis, astrocytes in culture directly synthesize lactate from extracellular glucose (Walz and Mukerji, 1998a,b) suggesting that astrocytes may convert blood glucose into lactate through glycolysis. Moreover, this process seems to be regulated by synaptic activity, a fact consistent with the idea that astrocytes modulate glycolytic activity in synchrony with neuronal requirements of lactate (Bouzier-Sore et al., 2002).

Lactate synthesized by astrocytes can freely cross the plasma membrane and thus become available to neurons (Pellerin et al., 1998b). It has been shown that the transport of lactate into neurons is mediated by a specific carrier (Dringen et al., 1993; Tildon et al., 1993; MacKenna et al., 1998; Debernardi et al., 2003) and that these cells exhibit a high capacity for lactate utilization (Tabernero et al., 1993; Vicario et al., 1993). Lactate is also exported to the extracellular medium by astrocytes in the form of citrate or other tricarboxylic acid cycle (TCA) intermediates (Sonnewald et al., 1991; Westergaard et al., 1994; Giaume et al., 1997). Consequently, neurons show a high capacity for plasma lactate utilization because they are able to use lactate released by astrocytes (Fig. 1). This may explain why lactate is able to support neuronal activity

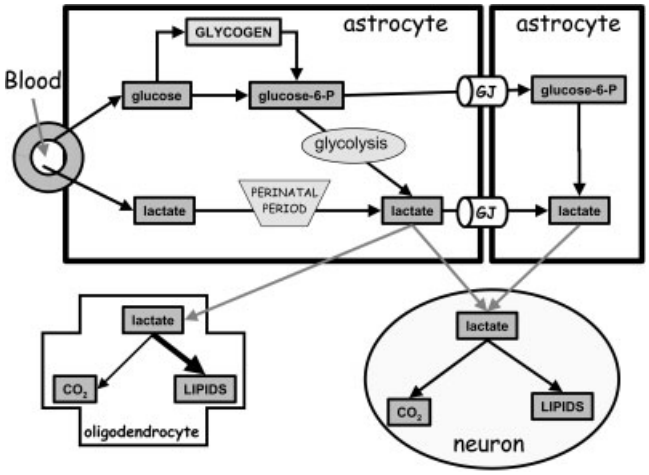

Fig. 1. Lactate metabolism in the brain. During the adult life, lactate is used as an exchangeable substrate among brain cells to maintain energy homeostasis in the CNS, supplying energy and carbon skeletons to neurons or oligodendrocytes. Because astrocytes lack glucose-6-phosphatase, glucose-6-phosphate would be transported to the adjacent astrocytes through gap junctions (GJ) or converted in lactate through glycolysis. During the perinatal period, lactate accumulated in fetal blood is metabolized rapidly immediately after delivery, presumably to meet the need for the energy and carbons skeletons required for proliferation and differentiation of brain cells.

(Bock et al., 1993; Izumi et al., 1994; Maran et al., 1994). In addition, during the postnatal period glucose availability is scarce but much lactate is supplied from the blood. Under these circumstances, lactate is therefore used by both neurons and astrocytes to sustain brain development. In this situation, however, glucose remains required by the brain for the generation of NADPH and glycerol-borne phospholipids. In agreement with this, when lactate is available widely both neurons and astrocytes use glucose for the synthesis of NADPH and ribose-5-phosphate in the pentose-phosphate shunt or the synthesis of glycerol-borne phospholipids (Tabernero et al., 1996b). Likewise, the ability of neurons and astrocytes to metabolize lactate, saving glucose for exclusive purposes, would explain why lactate is able to support cerebral function during episodes of hypoglycemia (Schurr et al., 1988; Bock et al., 1993; Izumi et al., 1994; Maran et al., 1994). Under conditions of hypoglycemia, lactate is thus presumably used to sustain the bulk of cellular energy and carbon expenditure whereas the scarce glucose available would be used for the exclusive purposes that cannot be fulfilled by lactate.

LACTATE PASSAGE THROUGH GAP JUNCTIONS

Gap junctions allow direct intercellular communication between the cytoplasm of neighboring cells. The ultrastructure of a junctional channel is now well established (Bennett et al., 1991), with each channel comprising a ring of six protein subunits called connexins (Peracchia et al., 1994; Bruzzone et al., 1996). The diffusion through

gap junctions of various energetic metabolites was evaluated by adapting the scrape-loading dye transfer technique (El-Fouly et al., 1987), using radioactive compounds and following their intercellular spread by autoradiography (Tabernero et al., 1996a). This technique was used to demonstrate that astrocytic gap junctions are freely permeable to glucose, glucose-6-phosphate (Fig. 1), glutamine, and glutamate (Tabernero et al., 1996a; Giaume et al., 1997). Astrocytic gap junctions are also permeable to lactate (Fig. 1), which may contribute to its diffusion through brain structures (Tabernero et al., 1996a). There is evidence suggesting that the passage of metabolites through astrocytic gap junctions can be finely regulated. In this context, we have shown (Granda et al., 1998) that gap junction permeability is controlled by the activity of the K-ATP channel. The K-ATP channel is composed of two subunits, the inwardly rectifying K^+ channel (KIR) and the sulfonylurea receptor (SUR) (Nicolino, 1997), the latter conferring the channel sensitivity to ATP and sulfonylureas. The existence of the K-ATP channel has been reported in the central nervous system (CNS) (Amoroso et al., 1990) and is sensitive to sulfonylureas (Niki and Ashcroft, 1993; Xia et al., 1993). Because sulfonylureas mimic the effects of ATP on the K-ATP channel, it may be proposed that intracellular ATP concentrations might regulate gap junction permeability (Vera et al., 1996) controlling the K-ATP channel. The energy status of the astrocyte would therefore be able to regulate intercellular communication through gap junctions. When the energy status of the astrocyte is sufficient to sustain its own metabolic machinery, gap junction permeability would increase to allow the passage of metabolites (Tabernero et al., 1996a; Giaume et al., 1997) to adjacent cells. If the energy reserves of the astrocyte were compromised, however, ATP concentrations would decrease, resulting in a drop in gap junction permeability (Vera et al., 1996). Consequently, we have suggested that astrocytic gap junctions play an important role in "pipelining" metabolic substrates through the CNS by acting like waterway locks that allow the establishment of a cell-to-cell metabolite gradient that fuels the transport of substrates to targeted neurons (Tabernero et al., 1996a; Giaume et al., 1997). Accordingly, ATP concentrations may regulate the open/closed state of the "locks" by controlling the activity of the K-ATP channel. Once the incoming substrates have fulfilled the energy requirements of the cells, gap junction permeability would increase to allow spared metabolic substrates to pass to adjacent cells, thus distributing energy and carbon skeletons through the CNS. If so, the K-ATP channel may play an important role in controlling the transport of ions, metabolites, and signals through the CNS, thus regulating the crucial collaboration between astrocytes and neurons.

LACTATE AS A SOURCE OF OLEIC ACID, A NEW NEUROTROPHIC FACTOR

The metabolic fate of lactate may be regulated by the presence of albumin in the blood because the presence of this protein in incubation medium increases the rate of lactate incorporation into lipids by isolated cells from early neonatal rat brain (Vicario et al., 1991). Moreover, in cultured astrocytes albumin strongly increases (by more than 100%) the flux of substrates through the pyruvate dehydrogenase (PDH)-catalyzed reaction (Tabernero et al., 1999). This effect is dose dependent and specific to albumin and is not mimicked by other proteins such as γ-globulin or compounds of similar molecular weight such as dextran. On the other hand, albumin only slightly stimulates other metabolic pathways such as the TCA cycle or the pentose phosphate pathway, indicating that the effect of albumin is specific and exerted on the reaction catalyzed by PDH. The presence of fatty acids, however, counteracts the effect of albumin, suggesting that albumin activates PDH by sequestrating free fatty acids or their CoA derivatives (Tabernero et al., 1999). Astrocytes internalize albumin in vesicle-like structures by receptor-mediated endocytosis (Tabernero et al., 2002). Albumin uptake is followed by transcytosis, including passage through the endoplasmic reticulum (ER), which is required to induce the synthesis of oleic acid. This clearly suggests that the transcytosis of albumin includes passage through the ER, where albumin sequestrates oleic acid, and the whole process initiating the signal cascade for the synthesis of oleic acid (Fig. 2).

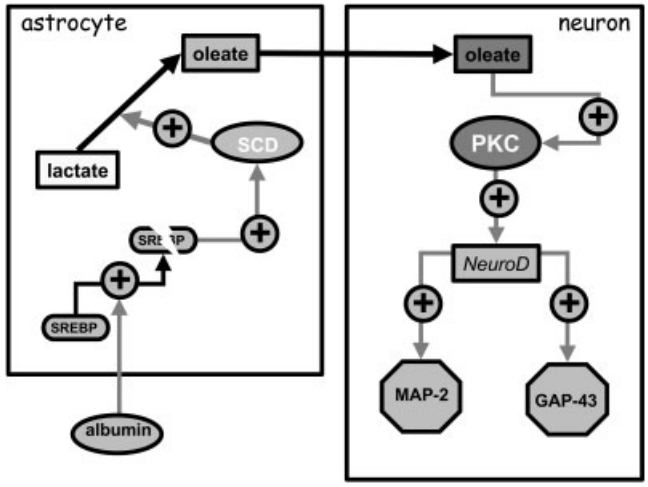

Fig. 2. Differentiation of neurons promoted by oleic acid synthesized and released by astrocytes. Albumin enters astrocyte by a receptor-mediated mechanism reaching endoplasmic reticulum in which promotes the hydrolysis and subsequent activation of sterol responding element binding protein-1 (SREBP) that induces the expression of sterol-CoA desaturase (SCD), a key enzyme in oleic acid (oleate) synthesis. Oleic acid is released by astrocytes reaching neurons in which promotes the expression of microtubule associated protein-2 (MAP-2), a marker of dendrite growth, and of growth-associated protein-43 (GAP-43), a marker of axon growth, through the activation of protein kinase C (PKC) and the subsequent expression of transcription factor NeuroD2.

Oleic acid was the only fatty acid synthesized by astrocytes, suggesting that this phenomenon has a specific purpose. In fact, the single double bond of oleic acid is enough to sharply increase the fluidity of biological mem-

branes (Alberts et al., 1996). Because membrane fluidity is critical for neurons, incorporation of oleic acid-borne phospholipids into a discrete area of the membrane could substantially change membrane properties. In agreement with this, oleic acid is incorporated preferentially into neurite bases (Tabernero et al., 2001), suggesting that increased fluidity is required at the sites of newly emerging axons or dendrites. This would facilitate the sprouting of the membrane during neurite growth together with enhanced flexibility for axon orientation.

Growth associate protein-43 (GAP-43) is conspicuously present during brain development but its content decreases sharply in adult life, when the presence of GAP-43 is constrained to high-plasticity neuronal regions or certain exclusive synapses during long-term potentiation (Skene and Virág, 1989). Consequently, GAP-43 may play an important role in neuronal differentiation. In support of this, the presence of oleic acid significantly increases the synthesis of GAP-43, which is distributed along axonal structures (Tabernero et al., 2001). Indeed, the presence of oleic acid leads to the aggregation of neurons in the typical gray/white matter fashion observed in vivo. In addition, the presence of oleic acid elongated axons, which contacted other neurons, thus mimicking the neuronal networks observed in the CNS. This phenomenon is accompanied by an increase in the synthesis of GAP-43, which may play an important role in axonal build-up (Tabernero et al., 2001). The presence of oleic acid also upregulated microtubule associated protein-2 (MAP-2) a marker of dendrite growth (Fig. 2) (Rodríguez-Rodríguez et al., 2004), suggesting that oleic acid is a neurotrophic factor that promotes dendrite sprouting. It is therefore reasonable to propose that oleic acid promotes neuronal differentiation in culture.

LACTATE AS THE MAIN METABOLIC SUBSTRATE FOR OLIGODENDROCYTES

Because oligodendrocytes synthesize and maintain myelin in the CNS, these cells require metabolic substrates for the synthesis of this specialized lipid-rich membrane (for review, see Baumann and Pham-Dinh, 2001; Lee, 2001). In this context, we found that not only neurons and astrocytes are able to use lactate but also oligodendrocytes actively utilize lactate by oxidation and lipogenesis (Fig. 1). The rate of lactate utilization by oligodendrocytes was thus threefold higher than that observed in astrocytes and neurons (Sánchez-Abarca et al., 2001). The high rates of lactate utilization exhibited by oligodendrocytes were accounted for mainly by the lipogenesis rate, which was higher than the rates observed in other neural cells (Sánchez-Abarca et al., 2001). This was not unexpected because oligodendrocytes synthesize myelin, which requires active lipogenesis. It is therefore tempting to suggest that lactate from the blood or that synthesized by astrocytes from glycogen can be used for oligodendrocyte development, including myelin synthesis.

Oligodendrocytes also showed the maximum rate of glucose utilization as compared to astrocytes and neurons (Sánchez-Abarca et al., 2001). Again, oligodendrocytes showed high rates of glucose utilization by the pathways required for lipid synthesis. Oligodendrocytes thus exhibited a high rate of lipid synthesis together with a strong activity of the pentose phosphate pathway (Sánchez-Abarca et al., 2001), which provides redox power in the form of NADPH for lipid synthesis (Sykes et al., 1986). In addition, oligodendrocytes showed high rates of glucose oxidation through the pyruvate dehydrogenase-catalyzed reaction, a compulsory step in the generation of acetyl-CoA as a precursor for lipid synthesis. The rate of glycerol synthesis was also high in oligodendrocytes, suggesting that oligodendrocyte metabolism also provides glycerol for the synthesis of glycerol-borne phospholipids (Sánchez-Abarca et al., 2001). These results clearly suggest that oligodendrocyte metabolism is designed for the synthesis of myelin, which is a large and highly specialized lipid-enriched membrane.

CONCLUSIONS

It may be concluded that lactate is an important metabolic substrate for the brain. During adult life, it is used as an exchangeable substrate among brain cells to maintain energy homeostasis in the CNS, particularly during starvation, when astrocyte glycogen must be broken down to supply energy and carbon skeletons to neurons. In addition, lactate may also be synthesized in astrocytes from blood glucose to account for neuronal requirements during synaptic activity. Finally, lactate plays a crucial role in brain development during the perinatal period. Lactate from the mother and that synthesized in the placenta thus cross syncytiotrophoblast membranes through the monocarboxylate carrier to reach the fetal brain, which uses it as a metabolic substrate. Lactate accumulates in fetal blood at the end of gestation although it is metabolized rapidly immediately after delivery. In fact, neurons, astrocytes, and oligodendrocytes use lactate as preferential substrate, suggesting that lactate is essential for brain cell proliferation and differentiation. This may be relevant in humans, in which the key steps of brain development occur during the perinatal period.

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