Rose, C.F., 2010. Increase brain lactate in hepatic encephalopathy: Cause or consequence? *Neurochemistry international*, 57(4), p.389–394.

INCREASE BRAIN LACTATE IN HEPATIC ENCEPHALOPATHY: CAUSE OR CONSEQUENCE?

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ABSTRACT

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome which develops as a result of liver failure or disease. Increased concentrations of brain lactate (microdialysate, cerebrospinal fluid, tissue) are commonly measured in patients with HE induced by either acute or chronic liver failure. Whether an increase in brain lactate is a cause or a consequence of HE remains undetermined. A rise in cerebral lactate may occur due to (1) blood-borne lactate (hyperlactataemia) crossing the blood–brain barrier, (2) increased glycolysis due to energy failure or impairment and (3) increased lactate production/release or decreased lactate utilization/uptake. This review explores the different reasons for lactate accumulation in the brain during liver failure and describes the possible roles of lactate in the pathogenesis of HE.

Keywords
Hepatic encephalopathy; Lactate; Ammonia

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome which develops as a result of liver failure or disease. It is characterized by an array of neurological symptoms ranging from changes in personality, alterations in day–night rhythms, consciousness, concentration and attention, progressing to relentless cognitive, psychiatric and motor disturbances, coma and death (Butterworth and Vaquero, 2009). HE typically presents as one of 2 forms in association with (1) chronic liver failure/disease (CLF) or (2) acute liver failure (ALF). Brain edema is a common characteristic observed in ALF, believed to occur due to astrocyte swelling (Butterworth and Vaquero, 2009). Intracranial hypertension is a major complication developing principally in patients with ALF which consequently leads to brain stem herniation and 30% mortality (Shawcross and Jalan, 2005). Brain edema is also observed in the setting of CLF however contrary to ALF, intracranial hypertension is rarely seen (Häussinger, 2006).

Circulating neurotoxins which accumulate in brain as a consequence of liver failure/disease cause a number of effects on cerebral metabolism, creating a multiplicity of metabolic disturbances and encephalopathy (Felipo and Butterworth, 2002). Ammonia, produced mainly within the gut during protein digestion and amino acid deamination, is a neurotoxin believed to play a major role in the pathogenesis of HE. The concentration of ammonia in the blood is regulated by the urea cycle in the healthy liver and therefore liver failure/disease leads to hyperammonemia. Ammonia in aqueous solution is composed of gaseous (NH_3) and ionic (NH_4^+) components and the ratio of NH_3/NH_4^+ is derived from the Henderson-Hasselbalch equation (Cooper and Plum, 1987). As a gas, ammonia can easily diffuse across all membranes and since the ionic properties of NH4+ are very similar to K+, NH4+ is capable of crossing in and out of cells through K+ transporters and channels (Bosoi and Rose, 2009). A specific transporter for ammonia has recently been identified in the kidney however its role in the brain remains uncertain (Bakouh et al., 2006). With ammonia easily capable of crossing all cell membranes, an increase in blood ammonia leads to an increase in brain ammonia. The neurotoxicity of ammonia has been well documented, however the exact mechanisms by which ammonia exerts its pathological effects continue to be unanswered. In ALF, increased intracranial pressure (ICP) and brain stem herniation are related to arterial ammonia concentrations as demonstrated in both clinical studies (Bernal et al., 2007, Bhatia et al., 2006, Jalan et al., 2004 and Clemmesen et al.,

The final publication is available at http://dx.doi.org/10.1016/j.neuint.2010.06.012

1999) and animal experiments (Sen et al., 2006, Jover et al., 2006 and Rose et al., 1999). Hyperammonemia is a common characteristic of CLF (Butterworth et al., 2009) however whether the existence of a correlation between blood ammonia levels and grade (severity) of HE remains controversial (Kundra et al., 2005 and Ong et al., 2003).

Lactate, a product of glucose metabolism, is another factor believed to be implicated in the pathogenesis of HE however whether an increase in brain lactate is a cause or a consequence of HE is not fully resolved.

HYPERLACTATAEMIA

Hyperlactataemia is observed in patients with ALF (Walsh et al., 1999 and Saibara et al., 1994) and blood lactate levels have been suggested as a prognostic marker in patients with either acetaminophen-induced (Bernal et al., 2002 and Schmidt and Larsen, 2003) and non-acetaminophen-induced (Funk et al., 2006 and Dabos et al., 2004) ALF. Furthermore, blood lactate has also been found to be independently associated with mortality in seriously ill cirrhotic patients (Zauner et al., 2000) as well as many other critical illnesses (Mizock and Falk, 1992).

Different animal models of ALF have also demonstrated an increase in blood lactate. ALF induced by hepatic devascularisation/ischemia in both pigs (Rose et al., 2007) and rats (Zwingmann et al., 2003, Chatauret et al., 2003, Mans et al., 1994 and Bosman et al., 1990) leads to hyperlactataemia. ALF caused by carbon tetrachloride hepatotoxicity leads to increased blood lactate (Bates et al., 1989) a finding which is also observed in urease-injected (Bosman et al., 1990) and acute ammonia-injected (Fitzpatrick et al., 1989) rats.

Traditionally, an increase in lactate is believed to be a result of energy failure or impairment and increased anaerobic metabolism due to cellular hypoxia. This may be of importance in the setting of liver failure (Subramanian and Kellum, 2000) however numerous other reasons for increased blood lactate in liver failure/disease exist. It is important to note that elevated blood lactate concentrations do not always indicate tissue hypoxia (Clemmesen et al., 2000 and Walsh et al., 1998). Circulating lactate is normally metabolised in the liver to glucose (gluconeogenesis) and therefore impaired hepatic function will decrease the elimination and prolong the half-life of lactate, leading to hyperlactataemia (Levraut et al., 1998 and Woll and Record, 1979). An increase in blood lactate may also arise due to necrotic hepatocytes expelling their intracellular contents (including lactate) (Clemmesen et al., 2000). Moreover, the levels of blood lactate are further elevated upon the onset of multi-organ-failure during liver failure/disease through organ-failure lactate leakage. In summary, hyperlactataemia in liver failure/disease may arise from (i) decreased hepatic lactate metabolism, (ii) increased hepatic lactate production due to energy failure or impairment and/or (iii) increased release due to hepatocyte necrotic cell death (Schmidt and Larsen, 2006 and Murphy et al., 2001).

INCREASED BRAIN LACTATE

Increased brain lactate is a consistent finding in various animal models of ALF (Rose et al., 2007, Zwingmann et al., 2003, Chatauret et al., 2003, Nyberg et al., 1998, Mans et al., 1994, Bates et al., 1989, Holmin et al., 1983 and Hawkins et al., 1973) and has been reported to parallel changes in encephalopathy defined by shifts in electroencephalography (Bosman et al., 1990). Normal and portacaval shunted rats following acute injections of ammonia become severely encephalopathic and experience an increase in brain lactate (Therrien et al., 1997, Fitzpatrick et al., 1989 and Hindfelt et al., 1977). Cerebral microdialysis, an *in vivo* technique to monitor the metabolism and biochemistry of the extracellular compartment in a defined region of the brain, is an excellent method to define the temporal resolution of changes in cerebral metabolites (with successive sampling of microdialysates) in relation to changes in encephalopathy. In pigs with ALF, induced by hepatic devascularisation/ischemia, microdialysate lactate increased in association with increased ICP (Rose et al., 2007). Clinically, cerebral microdialysis has become a well-established technique in many intensive care units (Ungerstedt and Rostami, 2004 and Hutchinson et al., 2000) and the group of Dr. Fin Stolze Larsen from Copenhagen, Denmark

have done remarkable studies monitoring the extracellular space in parallel with changes in ICP in the brains of patients with ALF. His group has shown an increase in microdialysate (extracellular) lactate in the frontal cortex of patients with ALF correlates with an increase in ICP and preceeds surges in high ICP (Tofteng and Larsen, 2002).

In addition to ALF, concentrations of lactate in cerebrospinal fluid (CSF) are also elevated in patients with cirrhosis and CLF however only in those with overt HE (>grade 2), reflecting the severity of the metabolic impairment of the brain (Yao et al., 1987).

BRAIN EDEMA AND CEREBRAL LACTATE

Elevated brain lactate concentrations have been suggested to contribute to the pathogenesis of brain edema, a common finding in ALF and due to newly advanced imaging techniques, is also observed in patients with CLF (Rovira et al., 2008, Sugimoto et al., 2008 and Häussinger, 2006). Evidence has developed from in vitro studies where cultured astrocytes exposed to lactate significantly swell (Ringel et al., 2006 and Staub et al., 1990). Furthermore, the highest concentration of CSF lactate in rats with ALF is found during coma stages when brain edema is present (Chatauret et al., 2003). Additionally in the same ALF model, using nuclear magnetic resonance spectroscopy, an increase in de novo synthesis of lactate from glucose (13C-Glc) in brain correlates with severity of encephalopathy and brain edema (Zwingmann et al., 2003). In another model of ALF, brain lactate concentrations, determined by magnetic resonance spectroscopy were found elevated in d-galactosamine-induced ALF and associated with intracranial hypertension and poor neurological outcome (Nyberg et al., 1998). Recently, Chavarria et al. (2010) demonstrated using magnetic resonance techniques, that a shift in HE from pre-coma to coma stage (associated with development of brain edema) in rats with ALF was accompanied with a marked increase in cerebral lactate.

Therapeutic interventions, such as mild hypothermia and albumin dialysis, have helped our understanding in the pathogenesis of brain edema in ALF. Rats with ALF (hepatic devascularisation/ischemia) cooled to 35°C demonstrated an attenuation in CSF ammonia and lactate along with a normalisation of brain edema (Chatauret et al., 2003). Also, ALF pigs treated with molecular adsorbents recirculating system (MARS), demonstrated an attenuation in ICP, brain edema and extracellular ammonia and lactate (Rose et al., 2007 and Sen et al., 2006). These studies describe the importance of cerebral ammonia and lactate in the pathogenesis of brain edema in ALF, however do not conclude whether ammonia and lactate are regulated independently.

LACTATE METABOLISM IN THE BRAIN

Lactate is produced from the metabolism of glucose through glycolysis. It is specifically generated and metabolised by the enzyme lactate dehydrogenase (LDH) in which the direction of the reaction is governed by the concentration of lactate, pyruvate and NADH/NAD^+ ratio (Fig. 1). LDH is found in both neurons and astrocytes, as isoenzymes LDH1 and LDH5 respectively. It is traditionally believed lactate is an end product of anaerobic glycolysis however there is increasing evidence suggesting lactate is a principal product of glycolysis (even in the presence of oxygen) and also a secondary fuel for the tricarboxylic acid cycle since lactate demonstrated to be an important cerebral oxidative energy substrate (for review see Pellerin et al., 2007 and Schurr, 2006).

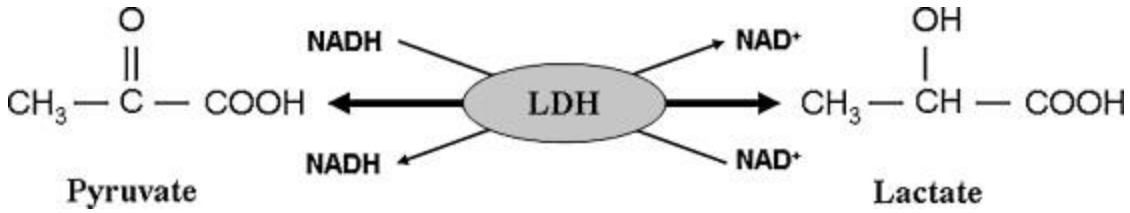

Fig. 1. Lactate dehydrogenase (LDH) catalyzes the reversible interconversion of pyruvate (+NADH) and lactate (+NAD^+).

LACTATE TRANSPORT IN THE BRAIN

Lactate is transported across cell membranes through different monocarboxylate transporters (MCTs), each with different K_m and V_{max} values. MCTs are symporters which co-transport lactate, through facilitated diffusion with H+. MCTs are bidirectional and the direction of lactate transport depends upon the H+ gradient (Bröer et al., 1999). Lactate transport therefore affects and is affected by fluxes in pH (Barros and Deitmer, 2010). Lactate is also capable of crossing cell membranes as lactic acid by simple diffusion (Juel, 1997) however since lactate has a pKa of 3.8, the ratio of lactate ion to non-dissociated lactic acid equals close to 3000/1 (at pH 7.3) therefore the amount of diffusible lactic acid is insignificant.

MCT isoforms, MCT1 and MCT4, are both expressed in astrocytes (Pierre and Pellerin, 2005 and Bergersen et al., 2002). There has been some controversy concerning the expression of MCT2 in astrocytes in vitro (Debernardi et al., 2003, Hanu et al., 2000 and Tildon et al., 1993) and in vivo (Gerhart et al., 1998 and Gerhart et al., 1997) however most evidence to date suggests MCT2 is expressed in neurons (Pierre and Pellerin, 2005 and Bergersen et al., 2002). Since MCT2 (neuronal) has a Km of 0.5 mM and MCT1 and MCT4 (astrocytic) have a Km of 3–5 mM and 15–30 mM respectively, this illustrates the importance of LDH activity in supporting and protecting neurons under certain pathophysiological conditions (see section lactate as an energy source below). Overall, neurons are better equipped to transport and use lactate as an energy source in comparison to astrocytes. A good example was recently described by Barros and Deitmer (2010) where decreasing the extracellular lactate from 2 mM to 1 mM caused a 42% decrease in lactate influx in MCT1-expressing astrocytes (Km of 3–5 mM) and only a 17% decrease in MCT2-expressing neurons (Km of 0.5 mM). Overall, increased lactate uptake of MCT2 is associated with increased intracellular lactate metabolism (Barros and Deitmer, 2010).

LACTATE AS AN ENERGY SOURCE

Since the astrocyte-neuron lactate shuttle hypothesis (ANLSH) was proposed by Pellerin and Magistretti (1994), many studies have documented and supported this hypothesis in which lactate synthesized within astrocytes is released (shuttled) into the interstitial space and used as a supplementary fuel (in addition to glucose) for neurons (for review see Pellerin et al., 2007). The bulk of ANLSH has been developed based on in vitro studies but has also been supported with in vivo studies (Hyder et al., 2006 and Serres et al., 2005). The ANLSH hypothesis has revolutionized the role of lactate in oxidative metabolism and has depicted energy metabolism between neurons and astrocytes is dissimilar. It has previously been demonstrated LDH1 in neurons expresses a higher affinity for lactate than LDH5 in astrocytes (Bittar et al., 1996). It is now known that astrocytes release lactate at a greater rate than neurons (Walz and Mukerji, 1988), that lactate is efficiently oxidized by neurons (Pellerin, 2003) and that lactate is the preferred oxidative substrate over glucose (Schurr, 2006, Tekkök et al., 2005 and Bouzier-Sore et al., 2003). Upon glutamate activation, glucose transport and utilization increases in astrocytes (Loaiza et al., 2003 and Pellerin and Magistretti, 2004) but decreases in neurons (Porras et al., 2004) even though energy demands increase. This favours lactate oxidation in neurons (Pellerin et al., 2007). Astrocytes can afford to produce lactate from pyruvate since glutamate taken up by high affinity transporters in the astrocytes may also be used to fuel the tricarboxylic acid cycle and oxidative metabolism (Hertz, 2004). It is important to note, glucose and lactate are integral and important entities of energy metabolism (Schurr, 2006) and that glycolysis is necessary to ensure proper cell function (Bak et al., 2006 and Ikemoto et al., 2003).

Traditionally glucose is thought to be the sole metabolic fuel for brain cells and this remains true even if lactate is used as an energy source, since lactate production originates from blood-borne glucose. Therefore the oxidation of lactate should stimulate the oxidation of glucose and not spare glucose (Schurr, 2006). Glucose provided by the blood is taken up by the astrocytes (due to the morphological distribution of astrocytes in the blood–brain barrier) and is predominantly oxidized to lactate which is released into the synaptic cleft, taken up by neurons and used as an

energy source. The concept of a "lactate flow" from astrocytes to neurons is logical considering the differential expression of MCTs isoforms and LDHs isoenzymes (and their respective differential affinities) in neurons and astrocytes.

EXPLANATIONS FOR INCREASED BRAIN LACTATE

FROM THE BLOOD

The same way hyperammonemia leads to increased brain ammonia, it is often debated whether hyperlactataemia leads to an increase in cerebral lactate. It has previously been demonstrated lactate cannot easily cross the blood–brain barrier (Hertz and Dienel, 2002 and Auer, 1986), infusing lactate intravenously does not increase CSF lactate (Alexander et al., 1962) and levels of blood and CSF lactate are regulated independently (Posner and Plum, 1967). However, others have documented that the blood–brain barrier is permeable to lactate (Dalsgaard et al., 2004, Smith et al., 2003 and Oldendorf, 1973) and the lactate transporter MCT1 is expressed on endothelial cells (Gerhart et al., 1997). Furthermore, Tofteng and Larsen (2002) in a case report describing a patient with severe ALF and brain edema found microdialysate (extracellular) lactate was influenced by alterations in arterial concentrations of lactate. However, an increase in extracellular lactate was associated with an increase in brain LDH activity in pigs with ALF (Rose et al., 2007) suggesting increased brain derived lactate. Therefore, in the context of liver failure/disease where the blood–brain barrier may be compromised, the relationship between blood and brain lactate remains undefined.

A MARKER FOR ENERGY IMPAIRMENT

There is a lot of evidence demonstrating that an increase in cerebral lactate is a consequence of intrinsic cellular metabolic changes (Zwingmann et al., 2003). The neurotoxic mechanisms of ammonia are numerous and many have demonstrated to interfere with several energy metabolic pathways. Ammonia has shown to increase glycolysis by stimulating phosphofructokinase (Abrahams and Younathan, 1971 and Lowry and Passonneau, 1966), a key glycolytic enzyme. Also, ammonia has been shown to inhibit the rate-limiting tricarboxylic acid cycle enzyme α-ketoglutarate dehydrogenase (Lai and Cooper, 1986) which may be a protective mechanism for replenishing the astrocytic glutamate pool and subsequently detoxify ammonia through the astrocyte specific enzyme, glutamine synthetase (Cooper and Plum, 1987). These pathophysiological mechanisms interfere with energy metabolism leading to compromised brain energy metabolism as well as an increase in lactate formation. It has been postulated that an increase in cerebral lactate may be an indicator of impending energy failure secondary to injury to the mitochondria (Norenberg et al., 2005). Although the pathophysiological mechanisms listed above suggest energy failure, there is little evidence demonstrating high-energy phosphate compounds are reduced in the pathogenesis of HE. Normal rats acutely injected with ammonia develop an increase in brain lactate without affecting levels of ATP (Fitzpatrick et al., 1989, Lin and Raabe, 1985 and Hawkins et al., 1973). Different in vivo models of ALF demonstrating increased cerebral lactate and changes in electroencephalography did not show a decrease in high-energy phosphates (Mans et al., 1994, Bates et al., 1989, Friolet et al., 1989 and Deutz et al., 1988). Rats following a 5-week portacaval anastomosis, a model of chronic HE, characterized by hyperammonemia and increased brain ammonia, are accompanied with an increase in cerebral lactate but a preserved energy state (Holmin and Siesjö, 1974). These same animals, following an acute ammonia injection fall into coma which is associated with an increase in brain lactate and a decrease in brain ATP. In this same study, pre-coma stages were associated with an increase in cerebral lactate however no change in cerebral ATP (Hindfelt et al., 1977).

In summary, an increase in cerebral lactate does not reflect a decrease in high-energy phosphates in liver disease/failure. Evidence to date depicts brain energy impairment is secondary to ammonia metabolism and seems to occur in association with severe HE.

Cerebral lactate metabolism

An increase in extracellular lactate, measured using cerebral microdialysis, is observed in different animal models of ALF as well as patients with ALF (Rose et al., 2007 and Tofteng and Larsen, 2002). An increase in extracellular lactate is a result of either (i) over-production and/or over-release of lactate from cells or (ii) a decrease of lactate uptake into cells. Following the ANLSH which states neurons are better equipped than astrocytes in transporting (contain MCT2; higher affinity) and utilizing (contain LDH1; higher affinity) lactate as an energy source, an increase in extracellular lactate may reflect a decrease in neuronal lactate uptake/utilization, leading to neuronal dysfunction and encephalopathy. ALF pigs treated with albumin dialysis (MARS) demonstrated a decrease in extracellular lactate but LDH activity was unaffected and remained high compared to sham (Rose et al., 2007). This suggests attenuation in extracellular lactate is not due to decreased LDH activity. This implies a decrease of lactate from the extracellular space may be due to increased utilization of lactate by neurons. This would lead to well-fuelled, healthy functional neurons possibly reflected with attenuation of ICP (Rose et al., 2007). Increased neuronal utilization of lactate could occur as a result of lowering brain ammonia, which was also achieved following MARS treatment. The role of ammonia in neuronal and astrocytic lactate metabolism needs to be clarified and therefore future experiments are warranted.

Effects of increased brain lactate

Elevated levels of brain lactate can lead to lactic acidosis and subsequently a drop in pH. Acidosis can be detrimental to cellular function having a negative impact on metabolism (Kaila and Ransom, 1998). Furthermore, lactic acidosis has demonstrated to cause astrocytes to swell in vitro (Ringel et al., 2006 and Staub et al., 1990) and knowing acidosis alone can induce astrocyte swelling (Kempski et al., 1988) there is evidence that specific lactic acid swelling-induced properties exist. This includes the accumulation of intracellular lactate inside the astrocyte and rendering the cytoplasm hypertonic (Staub et al., 1990). A change in pH influences lactic acid levels and lactic acid levels affect pH. Additionally, ammonia influences pH and the ratio NH_3/NH_4^+ is dependent upon pH (Rose et al., 2005 and Cooper and Plum, 1987). The relationships between and dependencies of pH, ammonia and lactate (lactic acid) are complex and remain unresolved in the pathogenesis of HE. Whether an increase in cerebral lactate dependently or independently of ammonia leads to astrocyte swelling and/or acidosis remains to be determined. Andersson et al. (2009) have suggested the neurotoxic effects of ammonia vs lactate on astroglial dysfunction are different but this has yet to be confirmed in vivo.

In summary, increased brain lactate is observed in both patients and experimental animals with ALF in association with increased ICP. Increased brain lactate is also observed in CLF in both patients with overt signs of HE and animals with ammonia-precipitated severe encephalopathy. This suggests an increase in brain lactate occurs in association with the progression and severity of HE. An increase in cerebral lactate may arise due to blood-borne derived lactate (hyperlactataemia), increased glycolysis and/or energy impairment and increased lactate production/release or decreased lactate utilization/uptake (energy deprived neurons). It is inconclusive whether one of these pathophysiological mechanisms alone or all three are implicated in the development of HE. Finally an increase in cerebral lactate may not only be a consequence (marker) but also a cause in the pathogenesis of HE (Fig. 2).

The final publication is available at http://dx.doi.org/10.1016/j.neuint.2010.06.012

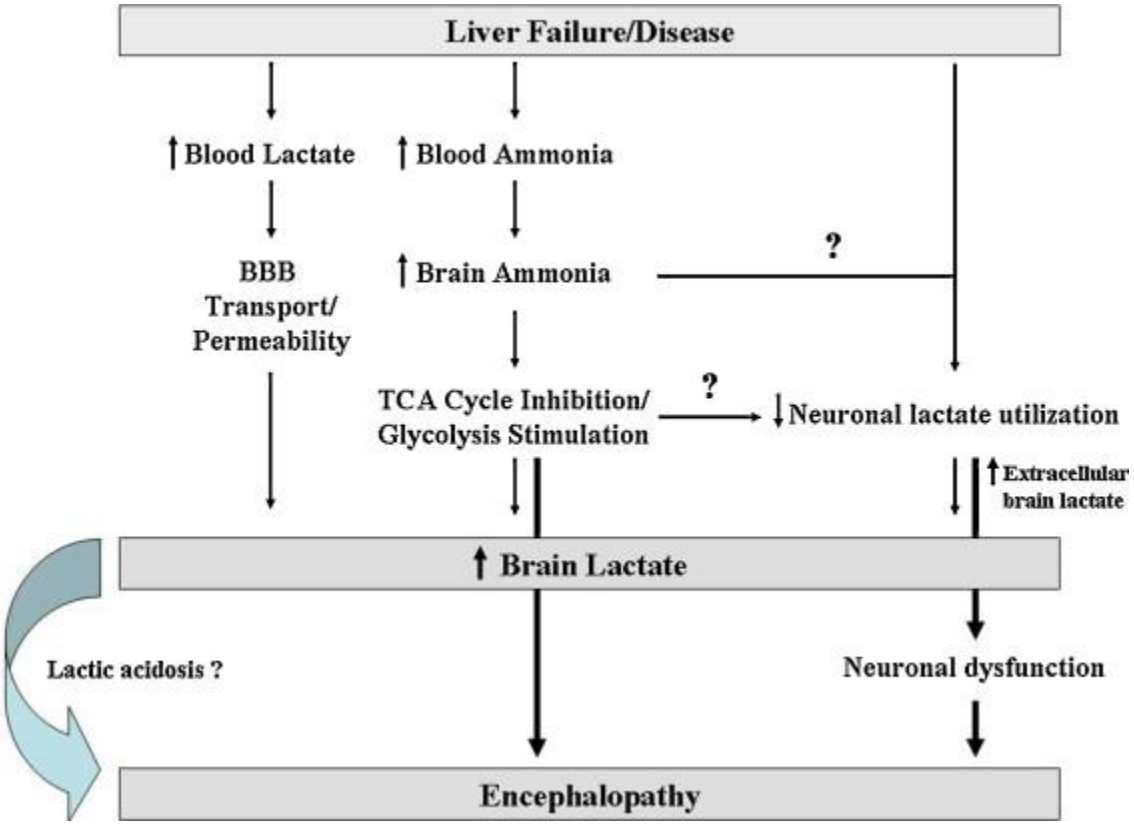

Fig. 2. Schematic summary describing the possible causes of increased brain lactate during liver failure and its role in the pathogenesis of hepatic encephalopathy.

REFERENCES

Abrahams, S.L., Younathan, E.S., 1971. Modulation of the kinetic properties of phosphofructokinase by ammonium ions. J. Biol. Chem 246, 2464–2467.

Alexander, S.C., Workman, R.D., Lambertsen, C.J., 1962. Hyperthermia, lactic acid infusion, and the composition of arterial blood and cerebrospinal fluid. Am J Physiol 202, 1049–1054.

Arias, I., 2009. The liver : biology and pathobiology, 5th ed. ed. Wiley-Blackwell, Chichester UK ;;Hoboken NJ.

Auer, R.N., 1986. Progress review: hypoglycemic brain damage. Stroke 17, 699–708.

Bak, L.K., Schousboe, A., Waagepetersen, H.S., 2006. The glutamate/GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer. J Neurochem 98, 641–653.

Barros, L.F., Courjaret, R., Jakoby, P., Loaiza, A., Lohr, C., Deitmer, J.W., 2009. Preferential transport and metabolism of glucose in Bergmann glia over Purkinje cells: a multiphoton study of cerebellar slices. Glia 57, 962–970.

Barros, L.F., Deitmer, J.W., 2010. Glucose and lactate supply to the synapse. Brain Res Rev 63, 149–159.

Bates, T.E., Williams, S.R., Kauppinen, R.A., Gadian, D.G., 1989. Observation of cerebral metabolites in an animal model of acute liver failure in vivo: a 1H and 31P nuclear magnetic resonance study. J Neurochem 53, 102–110.

Bergersen, L., Rafiki, A., Ottersen, O.P., 2002. Immunogold cytochemistry identifies specialized membrane domains for monocarboxylate transport in the central nervous system. Neurochem Res 27, 89–96.

Bernal, W., Auzinger, G., Sizer, E., Wendon, J., 2008. Intensive care management of acute liver failure. Semin Liver Dis 28, 188–200.

Bernal, W., Donaldson, N., Wyncoll, D., Wendon, J., 2002. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 359, 558–563.

Bhatia, V., Singh, R., Acharya, S.K., 2006. Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut 55, 98–104.

The final publication is available at http://dx.doi.org/10.1016/j.neuint.2010.06.012

Bittar, P.G., Charnay, Y., Pellerin, L., Bouras, C., Magistretti, P.J., 1996. Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. J Cereb Blood Flow Metab 16, 1079–1089.

Bosman, D.K., Deutz, N.E., Graaf, A.A.D., Hulst, R.W. vd, Eijk, H.M.V., Bovée, W.M., Maas, M.A., Jörning, G.G., Chamuleau, R.A., 1990. Changes in brain metabolism during hyperammonemia and acute liver failure: results of a comparative 1H-NMR spectroscopy and biochemical investigation. Hepatology 12, 281–290.

Bouzier-Sore, A.-K., Voisin, P., Canioni, P., Magistretti, P.J., Pellerin, L., 2003. Lactate is a preferential oxidative energy substrate over glucose for neurons in culture. J Cereb Blood Flow Metab 23, 1298–1306.

Bröer, S., Bröer, A., Schneider, H.P., Stegen, C., Halestrap, A.P., Deitmer, J.W., 1999. Characterization of the high-affinity monocarboxylate transporter MCT2 in Xenopus laevis oocytes. Biochem. J 341 (Pt 3), 529–535.

Butterworth, R.F., Norenberg, M.D., Felipo, V., Ferenci, P., Albrecht, J., Blei, A.T., HE, M. of the I.C. on E.M. of, 2009. Experimental models of hepatic encephalopathy: ISHEN guidelines. Liver Int 29, 783–788.

Chatauret, N., Zwingmann, C., Rose, C., Leibfritz, D., Butterworth, R.F., 2003. Effects of hypothermia on brain glucose metabolism in acute liver failure: a H/C-nuclear magnetic resonance study. Gastroenterology 125, 815–824.

Chavarria, L., Oria, M., Romero-Gimenez, J., Alonso, J., Lope-Piedrafita, S., Cordoba, J., 2010. Diffusion Tensor Imaging Supports the Cytotoxic Origin of Brain Edema in a Rat Model of Acute Liver Failure. Gastroenterology 138, 1566–1573.

Clemmesen, J.O., Høy, C.E., Kondrup, J., Ott, P., 2000. Splanchnic metabolism of fuel substrates in acute liver failure. J Hepatol 33, 941–948.

Clemmesen, J.O., Larsen, F.S., Kondrup, J., Hansen, B.A., Ott, P., 1999. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 29, 648–653.

Dabos, K.J., Newsome, P.N., Parkinson, J.A., Mohammed, H.H., Sadler, I.H., Plevris, J.N., Hayes, P.C., 2004. Biochemical prognostic markers of outcome in non-paracetamol-induced fulminant hepatic failure. Transplantation 77, 200–205.

Dalsgaard, M.K., Quistorff, B., Danielsen, E.R., Selmer, C., Vogelsang, T., Secher, N.H., 2004. A reduced cerebral metabolic ratio in exercise reflects metabolism and not accumulation of lactate within the human brain. J Physiol 554, 571–578.

Debernardi, R., Pierre, K., Lengacher, S., Magistretti, P.J., Pellerin, L., 2003. Cell-specific expression pattern of monocarboxylate transporters in astrocytes and neurons observed in different mouse brain cortical cell cultures. J Neurosci Res 73, 141–155.

Deutz, N.E., Chamuleau, R.A., Graaf, A.A. de, Bovée, W.M., Beer, R. de, 1988. In vivo 31P NMR spectroscopy of the rat cerebral cortex during acute hepatic encephalopathy. NMR Biomed 1, 101–106.

Fitzpatrick, S.M., Hetherington, H.P., Behar, K.L., Shulman, R.G., 1989. Effects of acute hyperammonemia on cerebral amino acid metabolism and pHi in vivo, measured by 1H and 31P nuclear magnetic resonance. J Neurochem 52, 741–749.

Friolet, R., Colombo, J.P., Lazeyras, F., Aue, W.P., Kretschmer, R., Zimmermann, A., Bachmann, C., 1989. In vivo 31P NMR spectroscopy of energy rich phosphates in the brain of the hyperammonemic rat. Biochem Biophys Res Commun 159, 815–820.

Funk, G.-C., Doberer, D., Fuhrmann, V., Holzinger, U., Kitzberger, R., Kneidinger, N., Lindner, G., Schneeweiss, B., 2006. The acidifying effect of lactate is neutralized by the alkalinizing effect of hypoalbuminemia in non-paracetamol-induced acute liver failure. J Hepatol 45, 387–392.

Gerhart, D.Z., Enerson, B.E., Zhdankina, O.Y., Leino, R.L., Drewes, L.R., 1997. Expression of monocarboxylate transporter MCT1 by brain endothelium and glia in adult and suckling rats. Am J Physiol 273, E207–E213.

Gerhart, D.Z., Enerson, B.E., Zhdankina, O.Y., Leino, R.L., Drewes, L.R., 1998. Expression of the monocarboxylate transporter MCT2 by rat brain glia. Glia 22, 272–281.

Hanu, R., McKenna, M., O'Neill, A., Resneck, W.G., Bloch, R.J., 2000. Monocarboxylic acid transporters, MCT1 and MCT2, in cortical astrocytes in vitro and in vivo. Am J Physiol Cell Physiol 278, C921–C930.

Hawkins, R.A., Houghton, C.R., Williamson, D.H., 1973. Hepatic redox state and gluconeogenesis from lactate in vivo in the rat. Biochem J 132, 19–25.

Hertz, L., 2004. The astrocyte-neuron lactate shuttle: a challenge of a challenge. J Cereb Blood Flow Metab 24, 1241–1248.

Hertz, L., Dienel, G.A., 2002. Energy metabolism in the brain. Int Rev Neurobiol 51, 1–102.

Hindfelt, B., Plum, F., Duffy, T.E., 1977. Effect of acute ammonia intoxication on cerebral metabolism in rats with portacaval shunts. J Clin Invest 59, 386–396.

Holmin, T., Agardh, C.D., Alinder, G., Herlin, P., Hultberg, B., 1983. The influence of total hepatectomy on cerebral energy state, ammonia-related amino acids of the brain and plasma amino acids in the rat. Eur J Clin Invest 13, 215–220.

Holmin, T., Jóhannsson, H., Siesjö, B.K., 1974. Effects on cerebral energy state of arterial hypotension in rats with porta-caval anastomosis. Acta Physiol Scand 90, 345–357.

Holmin, T., Siesjö, B.K., 1974. The effect of porta-caval anastomosis upon the energy state and upon acid-base parameters of the rat brain. J Neurochem 22, 403–412.

Hutchinson, P.J., Al-Rawi, P.G., O'Connell, M.T., Gupta, A.K., Pickard, J.D., Kirkpatrick, P.J., 2000. Biochemical changes related to hypoxia during cerebral aneurysm surgery: combined microdialysis and tissue oxygen monitoring: case report. Neurosurgery 46, 201–5; discussion 205–6.

Hyder, F., Patel, A.B., Gjedde, A., Rothman, D.L., Behar, K.L., Shulman, R.G., 2006. Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. J Cereb Blood Flow Metab 26, 865–877.

Ikemoto, A., Bole, D.G., Ueda, T., 2003. Glycolysis and glutamate accumulation into synaptic vesicles. Role of glyceraldehyde phosphate dehydrogenase and 3-phosphoglycerate kinase. J Biol Chem 278, 5929–5940.

Juel, C., 1997. Lactate-proton cotransport in skeletal muscle. Physiol Rev 77, 321–358.

Kaila, K., Ransom, B.R., 1998. pH and brain function. Wiley-Liss, New York.

The final publication is available at http://dx.doi.org/10.1016/j.neuint.2010.06.012

Lai, J.C., Cooper, A.J., 1986. Brain alpha-ketoglutarate dehydrogenase complex: kinetic properties, regional distribution, and effects of inhibitors. J Neurochem 47, 1376–1386.
Levraut, J., Ciebiera, J.P., Chave, S., Rabary, O., Jambou, P., Carles, M., Grimaud, D., 1998. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157, 1021–1026.
Lin, S., Raabe, W., 1985. Ammonia intoxication: effects on cerebral cortex and spinal cord. J Neurochem 44, 1252–1258.
Loaiza, A., Porras, O.H., Barros, L.F., 2003. Glutamate triggers rapid glucose transport stimulation in astrocytes as evidenced by real-time confocal microscopy. J Neurosci 23, 7337–7342.
Lockwood, A.H., Yap, E.W., Wong, W.H., 1991. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J. Cereb. Blood Flow Metab 11, 337–341.
Lowry, O.H., Passonneau, J.V., 1966. Kinetic evidence for multiple binding sites on phosphofructokinase. J Biol Chem 241, 2268–2279.
Mans, A.M., DeJoseph, M.R., Hawkins, R.A., 1994. Metabolic abnormalities and grade of encephalopathy in acute hepatic failure. J Neurochem 63, 1829–1838.
Mizock, B.A., Falk, J.L., 1992. Lactic acidosis in critical illness. Crit Care Med 20, 80–93.
Murphy, N.D., Kodakat, S.K., Wendon, J.A., Jooste, C.A., Muiesan, P., Rela, M., Heaton, N.D., 2001. Liver and intestinal lactate metabolism in patients with acute hepatic failure undergoing liver transplantation. Crit Care Med 29, 2111–2118.
Nyberg, S.L., Cerra, F.B., Gruetter, R., 1998. Brain lactate by magnetic resonance spectroscopy during fulminant hepatic failure in the dog. Liver Transpl Surg 4, 158–165.
Oldendorf, W.H., 1973. Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. Am J Physiol 224, 1450–1453.
Ong, J.P., Aggarwal, A., Krieger, D., Easley, K.A., Karafa, M.T., Lente, F.V., Arroliga, A.C., Mullen, K.D., 2003. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 114, 188–193.
Pellerin, L., 2003. Lactate as a pivotal element in neuron-glia metabolic cooperation. Neurochem Int 43, 331–338.
Pellerin, L., Bouzier-Sore, A.-K., Aubert, A., Serres, S., Merle, M., Costalat, R., Magistretti, P.J., 2007. Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55, 1251–1262.
Pellerin, L., Magistretti, P.J., 1994. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci U S A 91, 10625–10629.
Pellerin, L., Magistretti, P.J., 2003a. Food for thought: challenging the dogmas. J Cereb Blood Flow Metab 23, 1282–1286.
Pellerin, L., Magistretti, P.J., 2003b. How to balance the brain energy budget while spending glucose differently. J Physiol 546, 325.
Pellerin, L., Magistretti, P.J., 2004. Neuroscience. Let there be (NADH) light. Science 305, 50–52.
Pierre, K., Pellerin, L., 2005. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. J. Neurochem 94, 1–14.
Porras, O.H., Loaiza, A., Barros, L.F., 2004. Glutamate mediates acute glucose transport inhibition in hippocampal neurons. J Neurosci 24, 9669–9673.
Posner, J.B., Plum, F., 1967. Independence of blood and cerebrospinal fluid lactate. Arch. Neurol 16, 492–496.
Ringel, F., Baethmann, A., Plesnila, N., 2006. Lactacidosis-induced glial cell swelling depends on extracellular Ca2+. Neurosci Lett 398, 306–309.
Rose, C., Davies, N.A., Ytrebø, L.M., Sen, S., Nedredal, G.I., Belanger, M., Revhaug, A., Jalan, R., 2007. Association of reduced extracellular brain ammonia, lactate, and intracranial pressure in pigs with acute liver failure. Hepatology 46, 1883–92.
Rose, C., Michalak, A., Rao, K.V., Quack, G., Kircheis, G., Butterworth, R.F., 1999. L-ornithine-L-aspartate lowers plasma and cerebrospinal fluid ammonia and prevents brain edema in rats with acute liver failure. Hepatology 30, 636–640.
Rovira, A., Alonso, J., Córdoba, J., 2008. MR imaging findings in hepatic encephalopathy. AJNR Am J Neuroradiol 29, 1612–1621.
Saibara, T., Maeda, T., Onishi, S., Yamamoto, Y., 1994. Plasma exchange and the arterial blood ketone body ratio in patients with acute hepatic failure. J Hepatol 20, 617–622.
Schmidt, L.E., Larsen, F.S., 2003. Blood lactate as a prognostic marker in acetaminophen-induced acute liver failure. Hepatology 37, 1199–1201.
Schmidt, L.E., Larsen, F.S., 2006. Prognostic implications of hyperlactatemia, multiple organ failure, and systemic inflammatory response syndrome in patients with acetaminophen-induced acute liver failure. Crit Care Med 34, 337–343.
Schurr, A., 2006. Lactate: the ultimate cerebral oxidative energy substrate? J Cereb Blood Flow Metab 26, 142–152.
Sen, S., Davies, N.A., Mookerjee, R.P., Cheshire, L.M., Hodges, S.J., Williams, R., Jalan, R., 2004. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver transplantation 10, 1109–19.
Sen, S., Felldin, M., Steiner, C., Larsson, B., Gillett, G.T., Olausson, M., Williams, R., Jalan, R., 2002. Albumin dialysis and Molecular Adsorbents Recirculating System (MARS) for acute Wilson's disease. Liver Transpl 8, 962–967.
Serres, S., Bezancon, E., Franconi, J.-M., Merle, M., 2005. Ex vivo NMR study of lactate metabolism in rat brain under various depressed states. J Neurosci Res 79, 19–25.
Smith, D., Pernet, A., Hallett, W.A., Bingham, E., Marsden, P.K., Amiel, S.A., 2003. Lactate: a preferred fuel for human brain metabolism in vivo. J Cereb Blood Flow Metab 23, 658–664.
Staub, F., Baethmann, A., Peters, J., Weigt, H., Kempski, O., 1990. Effects of lactacidosis on glial cell volume and viability. J Cereb Blood Flow Metab 10, 866–876.
Subramanian, S., Kellum, J.A., 2000. Limiting harm in the ICU. Minerva Anestesiol 66, 324–332.
Sugimoto, R., Iwasa, M., Maeda, M., Urawa, N., Tanaka, H., Fujita, N., Kobayashi, Y., Takeda, K., Kaito, M., Takei, Y., 2008. Value of the apparent diffusion coefficient for quantification of low-grade hepatic encephalopathy. Am. J. Gastroenterol 103, 1413–1420.

The final publication is available at http://dx.doi.org/10.1016/j.neuint.2010.06.012

Tekkök, S.B., Brown, A.M., Westenbroek, R., Pellerin, L., Ransom, B.R., 2005. Transfer of glycogen-derived lactate from astrocytes to axons via specific monocarboxylate transporters supports mouse optic nerve activity. J. Neurosci. Res 81, 644–652.

Therrien, G., Rose, C., Butterworth, J., Butterworth, R.F., 1997. Protective effect of L-carnitine in ammonia-precipitated encephalopathy in the portacaval shunted rat. Hepatology 25, 551–556.

Tildon, J.T., McKenna, M.C., Stevenson, J., Couto, R., 1993. Transport of L-lactate by cultured rat brain astrocytes. Neurochem Res 18, 177–184.

Tofteng, F., Larsen, F.S., 2002. Monitoring extracellular concentrations of lactate, glutamate, and glycerol by in vivo microdialysis in the brain during liver transplantation in acute liver failure. Liver Transpl 8, 302–305.

Tomsig, J.L., Gruenstein, E., Dimlich, R.V., 1991. Inhibition of lactate-induced swelling by dichloroacetate in human astrocytoma cells. Brain Res 568, 92–100.

Ungerstedt, U., Rostami, E., 2004. Microdialysis in neurointensive care. Curr Pharm Des 10, 2145–2152.

Walsh, T.S., Hopton, P., Philips, B.J., Mackenzie, S.J., Lee, A., 1998. The effect of N-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure. Hepatology 27, 1332–1340.

Walsh, T.S., McLellan, S., Mackenzie, S.J., Lee, A., 1999. Hyperlactatemia and pulmonary lactate production in patients with fulminant hepatic failure. Chest 116, 471–476.

Walz, W., Mukerji, S., 1988. Lactate release from cultured astrocytes and neurons: a comparison. Glia 1, 366–370.

Woll, P.J., Record, C.O., 1979. Lactate elimination in man: effects of lactate concentration and hepatic dysfunction. Eur J Clin Invest 9, 397–404.

Yao, H., Sadoshima, S., Fujii, K., Kusuda, K., Ishitsuka, T., Tamaki, K., Fujishima, M., 1987. Cerebrospinal fluid lactate in patients with hepatic encephalopathy. Eur Neurol 27, 182–187.

Zauner, C., Schneeweiss, B., Schneider, B., Madl, C., Klos, H., Kranz, A., Ratheiser, K., Kramer, L., Lenz, K., 2000. Short-term prognosis in critically ill patients with liver cirrhosis: an evaluation of a new scoring system. Eur J Gastroenterol Hepatol 12, 517–522.

Zwingmann, C., Chatauret, N., Leibfritz, D., Butterworth, R.F., 2003. Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [H-C] nuclear magnetic resonance study. Hepatology 37, 420–428.

The final publication is available at http://dx.doi.org/10.1016/j.neuint.2010.06.012