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ENERGY METABOLISM and HEPATIC ENCEPHALOPATHY

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1. Introduction:

Hepatic Encephalopathy (HE) is a major and debilitating neurological disorder occurring in patients with severe liver disease, in chronic or acute forms (Williams, 1973). A serious complication of liver failure that includes a spectrum of neuropsychiatric abnormalities. The disturbances could range from little effect on mood to coma. With wide range of manifestations, HE varies in its acute and chronic forms. Chronic HE, has mild distortions during its frame which includes mood alterations, intellectual capacity decline, muscles abnormalities (Jones and Weissenborn,1997). Acute HE has a high mortality rate around 80-90% because of inter-complications developed in duration that includes brain edema, rise of intercranial pressure, causing onset of abrupt clinical manifestations like seizures, in severe cases may lead to coma (Capocaccia and Angelico, 1991).

Pathophysiology of HE has always been a major area of concern with serious research ongoing, although molecular basis for neurological complication remains elusive, the role of ammonia has set its footmark and is strongly implicated in pathogenesis of HE (Norenberg et al., 2009). Astrocytes are most affected cells in brain which undergo swelling and other abnormalities due to effects on metabolism by glutamine synthetase as cerebral ammonia content depends entirely on this (Norenberg, 1987).

Along with different other pathogenic mechanism, one proposed mechanism is a disturbance of cerebral energy metabolism (Hindfelt and Seisjo,1970). Subsequent research carried out in various animal models indicated the amino acid disturbances; altered glucose utilization; rise in glycolysis; decreased metabolic cycles like TCA, by altered alpha ketoglutarate (α-KG) enzyme, caused from ammonia toxicity. Along with this malate aspartate shuttle undergoes impairment as well. With such disturbances, oxidative stress also shoots up affecting mitochondrial permeability and in turn affecting electron transport chain, brain axonal and dendritic growth (Butterworth, 2003; Copper and plum, 1987). Mitochondria plays the significant role as it generates energy to fuel up normal cellular functions (Zick et al., 2009). By the process of aerobic oxidative phosphorylation, neuronal cells suffice their energy needs (Hatefi, 1985).

There have been number of hypotheses proposed time and again including osmotic gliopathy theory, postulating how glutamine can act as a osmolyte and by decreasing water potential of cells can cause brain edema, “Trojan horse”, where glutamine act as trojan horse and carries ammonia across mitochondrial membrane (Rama Rao et al. 2012; Albrecht and Norenberg 2006)). focusing on how ammonia disturbs the metabolic rate in brain and alters different cycles causing stress rise. The energy state of cells is reflected by high energy phosphates such as nucleotide di and tri phosphates which are the energy currency of cells. All the cells maintain their energy requirements largely by maintain ionic balance and for neuronal cells, this maintenance is

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crucial as slight disturbance in such may lead to neuronal deaths. The ionic balance of cells depends greatly on the metabolic pathways making energy metabolism as a significant factor in pathophysiological contributions to HE.

Using different methods to perform various in vivo and invitro studies to examine energy failure in neuronal cells, different diagnostic instruments proved to be a course shifter like MRI, MRS, NMR making a bridge between clinical diagnostics and basic research (Cristina caudalbu, 2012).

2. Glycolysis and Glucose utilization:

Increased rate of glycolysis is an established phenomenon for both chronic and acute HE also in case of hyperammonia. Research has opened different possibilities on how such regulation is affected. Initially ammonia was believed to stimulate glycolysis by enhancing the activity of rate limiting step of glycolysis phosphofructokinase, PFK in the brain of normal rats (Muntz and Hurwitz, 1951) but, later it was reported in rat hyperammonic model that along with PFK, it increases the activity of aldolase, glyceraldehyde-3-phosphate dehydrogenase (G3PD),and pyruvate kinase i.e. various other glycolytic enzymes (Ratnakumari and Murthy, 1992, 1993). Congenital chronic hyperammonia induced in sparse-fur (spf) mouse model also showcased the high rate of glycolysis (Ratnakumari et al., 1992). As per theoreticalmodels, increased glycolysis must heighten the rate of TCA cycle as well but the end product three carbon product of glycolysis, pyruvate instead to being channelized to TCA moves in anaerobic pathway causing the rise of lactate (Rama Rao and Norenberg, 2012).

The cerebral metabolic rate for glucose (CMRglc) has consistently reported a decline in hepatic encephalopathic patients (Hazell and Butterworth, 1999) implicating hypermetabolism contribution towards various neuropsychiatric symptoms observed in HE. Though, some studies have shown varied results as well. In an animal model study, CMRglc was reported to a rise (Cruz and Duffy, 1983) or no change is reported in hyperammonemic rats as well (cruz and Dinel, 1984). Increased cerebral glucose was reported in spf mouse model suggesting a decrease in glucose utilization. The discrepancies reported might be due to some errors including the use of different animal models which may in part be responsible for conflicting results. An animal model of acute liver failure induced in rats by hepatic devascularization, whole brain cerebral glucose utilization was shown to decrease (Mans et al., 1994).

While such studies though formulate many relations but failed to form a correlation between changes in glucose metabolism and degree of HE. In a study increased glucose utilization was reported in cultured neural cells and astrocytes treated with ammonia caused increased alanine production deriving from pyruvate. (Leke et al., 2011). This might represent an additional pathway for ammonia detoxification in neurons.

Lactate metabolism:

The end-product formed via the glyoxalase system is D-lactate, by following glutathione-dependent detoxification of methylglyoxal, a highly reactive dicarbonyl compound mainly formed as a by-product of glycolysis. Presence of methylglyoxal is a pathogenic factor in neurodegenerative disease because precursor of advanced glycation end products (Krautwald and

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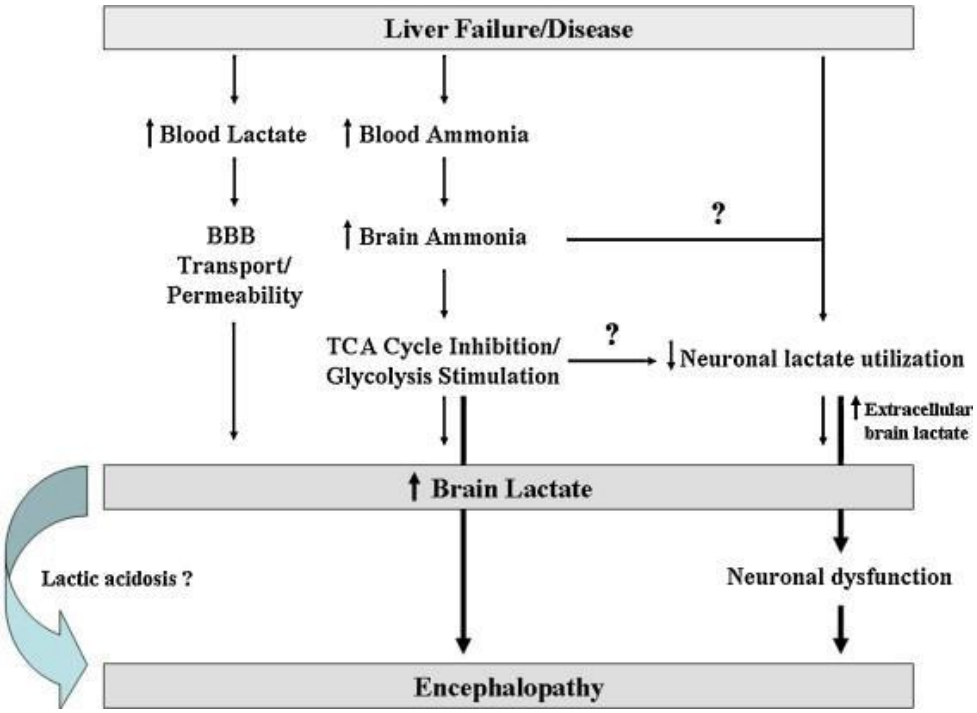
Munch, 2010). Henceforth, impairment of energy is marked by presence of increased lactate (Siesjo and Plum, 1971), while increased lactate in blood and brain is documented in case of HE and hyperammonemia as well (Walsh et al., 1999).Liver helps in the metabolism of muscle derived lactate, where it is converted to glucose and used to fuel all organ, including the muscle (Cori cycle) (Woll and Record 1979).

Though, glucose is considered as primary product for brain energy but, recent evidence suggests the capability of lactate to produce ATP by "astrocyte-neuron lactate shuttle" (ANLS), suggesting the production of lactate by astrocytes and is then released extracellularly where is taken up the neurons to fuel TCA (Schurr 2006; Pellerin et al. 2007). Since neuronal cell death is not described as a cardinal feature of HE, an increase in cerebral lactate is believed not to be a result of energy failure but instead is defined as impairment in cellular energy metabolism (Zwingmann 2007). The role of astrocytes is well established in HE pathology and studies with high lactate levels in ALF patients(Tofteng et al., 2002; Bjerring et al., 2010), suggests the possibility to use lactate as a prognostic marker for HE (Bernal et al., 2002). Studies also have demonstrated how cultured astrocytes show rise in lactate levels in presence of ammonia while a decline in pyruvate lactate ratio (Kala and Hertz, 2005). This indicates the impairment in TCA, ETC because of shortfall in availability of reducing equivalents (NAD and NADH).



Schematic summary describing the possible cause of increased brain lactate in HE pathogenesis (Rose, C.F., 2010)

Cerebral lactate homeostasis is maintained between lactate production/metabolism as well as release/uptake between astrocytes and neurons. This balance is important for the proper function of ANLS and metabolic impairment and/or transporter dysfunction can lead to alterations in lactate homeostasis and cellular dysfunction. Numerous microdialysis studies evidenced an increase in lactate levels in the extracellular compartment of the brain during ALF-induced HE

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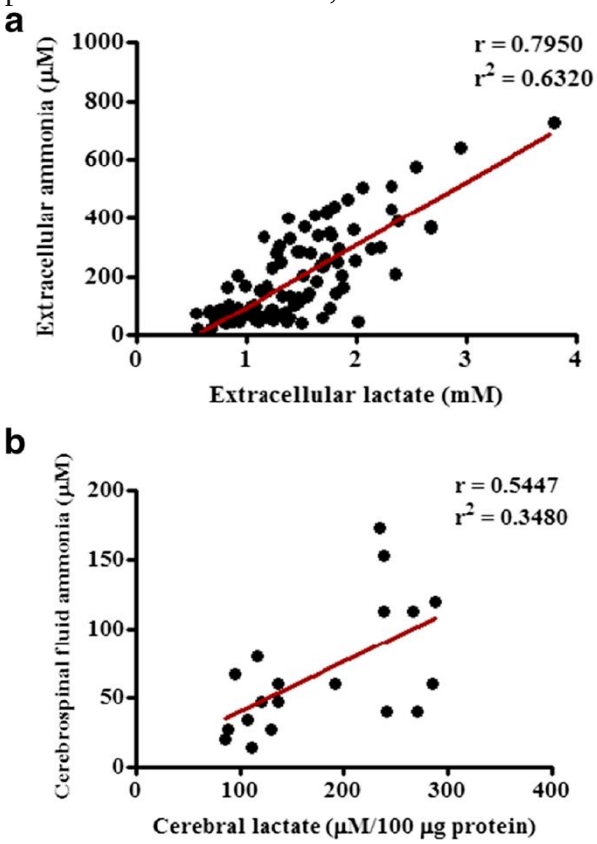
(Tofteng et al. 2002; Rose et al. 2007). This may be due to either an increase in astrocyte production and release or, a decrease in neuronal uptake and metabolism.



The graphs here represent the correlation between ammonia and lactate.

a. Represent the correlation in cerebral ammonia and lactate in pigs obtained by microdialysis.
b. Correlation between CSF and lactate in chronic liver disease induced by BDL in rats.

NMR studies evidenced lactate synthesis is dependent on the concentra- tion of ammonia (Zwingmann et al. 2003; Bosoi et al. 2014). To this regard, whether increased ammonia affects lactate homeostasis by modulating lactate transporters or enzymes remains to be elucidated in the future.

There is accumulating evidence that lactate plays an important role in the development of brain edema during ALF or CLD as previously reviewed (Bosoi and Rose 2013). The proposition that lactate may contribute to the brain edema in ALF was largely derived from previous observations that treatment of cultured astrocytes with lactic acid resulted in many adverse effects (Norenberg et al., 1987) including cell swelling (Lomneth et al., 1990; Staub et al., 1990; Andersson et al., 2009).

A study recently has obtained positive results by targeting lactate synthase inhibitor, dicholoroacetate (DCA) in BDL rats with brain edema, has seen the reduced cerebral lactate (Bosoi et al. 2014). This concludes lactate (possibly as a result from ammonia toxicity) plays an important role in the development of brain edema.

3. Bioenergetic changes and mitochondrial dysfunctions:

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3.1 TCA- cycle:

Brain utilizes most of free ammonia derived from blood to generate glutamate by glutamate dehydrogenase mediated reductive amination. The removal of α-KG required for glutamate generation (Bessman and Bessman, 1955) is based on this finding. However, a subsequent report suggested that inhibition of α-ketoglutarate dehydrogenase (α-KGDH) activity was responsible for increased α-KG levels in the CSF in rats with portacaval shunts (Shorey et al., 1967). Further studies showed that ammonia inhibited α-ketoglutarate dehydrogenase (α-KGDH) in mitochondria isolated from cerebral cortex (Lai and Cooper, 1991). Such inhibition of α-KGDH and the subsequent depletion of α-KG levels could profoundly affect the operational rate of TCA cycle and subsequently the electron transport chain. Taken together, it appears that a reduction in α-KGDH activity, the rate limiting enzyme in the TCA cycle, may adversely affect cerebral bioenergetics in acute and chronic HE.

3.2 Oxidative phosphorylation:

Early findings showcased the inhibition of stage III respiration in normal rats in case of ammonia addition isolated from cortex (Walshe et al., 1958; McKhann and Tower, 1961; Baraona et al., 1965). Establishing synergy with these findings, Kosenko et al., 1997 evidenced about inhibition of stage III respiration in brain mitochondria from acute-ammonia intoxicated rats. Inhibition of cytochrome C oxidase (complex IV of electron transport chain, ETC) activity and mRNA levels of its subunit II were observed in spf-mice (Rao et al., 1997). Additionally, a higher reduction of other ETC enzymes (complexes II and III) was observed in synaptosomes compared to non-synaptic mitochondria in spf-mice (Qureshi et al., 1998). CCl_4 induced ALF also showcased the inhibition of mitochondrial respiratory chain enzymes (I, III,IV) in cerebellum and cortex region of brain (Boer et al., 2009). Inhibition in Creatinine kinase as well is observed in different regions of brain.

3.3 High energy metabolites:

ATP and CK levels dropped down in portacaval-shunted rats infused with ammonia (Hindfelt et al., 1977). Recent studies have also indicated reduced levels of AMP and ADP in rats with acute hyperammonemia, and such decrease was found to be due to increased activity of AMP deaminase and adenosine deaminase (Kaminsky and Kosenko, 2010; Kosenko and Kaminsky, 2010). While a reduction in brain ATP levels observed in chronic HE and acute hyperammonemia could be due to inhibition of oxidative phosphorylation, it could also be due to its increased consumption. Studies have indeed shown increased activity of Na^+-K^+-ATPase in brains of rats with acute ammonia intoxication (Kosenko et al., 1994), and more recently in cultured astrocytes treated with ammonia (Xue et al. 2010).

3.4 Mitochondrial permeability transition (mPT):

The sudden increase in permeability of inner mitochondrial membrane for small solutes <1500 Da, includes ions and other molecules of this range. Other than the above

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mentioned reasons, mPT is another possible reason for energy metabolism impairment in HE. mPT may lead to collapse of mitochondrial membrane potential leading to pumping out of protons by ETC, leading to dysfunctioning of mitochondrial complexes and ROS generation Zoratti and Szabo, 1995; Bernardi et al., 1998; Norenberg and Rao, 2007). A recent study observed the induction of the mPT in brains of rats with ALF induced by hepatotoxin thioacetamide (RamaRao et al., 2010). While the reason for the absence of the mPT in neurons is not clear, one possibility could be differences in the susceptibility of neuronal and astrocytic mitochondria to the induction of the mPT. Oxidative/nitrosative stress (ONS), a major factor in the pathogenesis of acute and chronic HE (for reviews, see Norenberg et al., 2004 Jayakumar and Norenberg, 2011) is also a major inducer of the mPT (Castilho et al., 1995; Halestrap et al., 1997; Canevari et al., 2004). The chronology of events explains the divergent views on "Trojan horse hypothesis".

The generation of cytokines is a consequence of extensive liver necrosis as well as infection/ sepsis, a frequent complication of ALF (Williams and Smith, 1972; Wilkinson et al., 1974). Increased brain levels of TNF-α, IL-1β, and IL-6 were reported in experimental model of ALF (Jiang et al., 2009). We recently found that TNF- α, IL-1β, and IL-6 and IFN-γ significantly induced the mPT in cultured astrocytes.

4. Conclusion/Future perspectives:

Over time many studies have showcased the disturbance in various energy metabolic pathways in HE. Glycolysis and glucose utilization has shown to be increased in several models of rats with hyperammonia and in various animal models with HE which is believed to be due to rise in various glycolysis cycle enzymes such as PFK, G3PD, PK. Instead of a rise in TCA, a as rise in lactate is observed, this conversion was due to the inability of pyruvate to be channelled into the TCA cycle as PDH was shown to be inhibited by ammonia. Ammonia further can inhibit the activity of various enzymes like αKGDH and malate dehydrogenase activity, interfering with various metabolic activities in cells causing depletion of ATP and high energy metabolites in hyperammonemic patients. Many synergistic and conflicting studies are reported in various metabolic pathways. The interpretation of these findings is thus complicated by regional heterogeneity in energy metabolism observed in HE and hyperammonemia. Resolution of these inconsistencies will require an analysis of various pathways of energy metabolism, principally by the use of primary cultures of different neural cells.

Studies reporting that "energy enhancing" agents improve the clinical status, neuropsychiatric and behavioral abnormalities in patients and experimental animals with HE and hyperammonemia potentially highlights the importance of cerebral energy metabolism in the pathogenesis of HE and other hyperammonemic disorders. Consistent with these findings, recent studies have reported that treatment with L- carnitine or ALC improved cognitive functions and reduced behavioral abnormalities in patients with HE (Malaguarnera et al., 2008; Malaguarnera et al. 2010a; Malaguarnera et al. 2010b). In summary, *in vivo* studies employing various animal models, along with limited *in vitro* studies using cultured neurons and astrocytes treated with ammonia, demonstrates that cerebral energy metabolism is altered in both **acute and chronic models of** HE and hyperammonemia. Studies showing the induction of the mPT in ammonia-

treated cultured astrocytes, as well as in brains of rats with ALF suggest that the mPT plays a crucial role in the bioenergetic failure associated with HE and hyperammonemia. Targeting bioenergetic failure represents a potentially useful approach for the treatment of HE and other hyperammonemic disorders.

References:

Alvarez VM, Rama Rao KV, Brahmbhatt M, Norenberg MD. Interaction between cytokines and ammonia in the mitochondrial permeability transition in cultured astrocytes. J Neurosci Res. 2011 (in press).

Andersson AK, Adermark L, Persson M, Westerlund A, Olsson T, Hansson E. Lactate contributes to ammonia-mediated astroglial dysfunction during hyperammonemia. Neurochem Res. 2009; 34:556– 565. [PubMed: 18716864]

Astore D, Boicelli CA. Hyperammonemia and chronic hepatic encephalopathy: an in vivo PMRS study of the rat brain. MAGMA. 2000; 10:160–166. [PubMed: 10873206]

Bai G, Rama Rao KV, Murthy CR, Panickar KS, Jayakumar AR, Norenberg MD. Ammonia induces the mitochondrial permeability transition in primary cultures of rat astrocytes. J Neurosci Res. 2001; 66:981–991. [PubMed: 11746427]

Bélanger M, Yang J, Petit J-M et al (2011) Role of the glyoxalase system in astrocyte-mediated neuroprotection. J Neurosci Off J Soc Neurosci 31:18338–18352. doi:10.1523/JNEUROSCI.1249-11.2011

Bernal W, Donaldson N, Wyncoll D, Wendon J (2002) Blood lactate as an early predictor of outcome in paracetamol-induced acute liver fail- ure: a cohort study. Lancet 359:558–563. doi:10.1016/S0140- 6736(02)07743-7

Bosoi CR, Zwingmann C, Marin H et al (2014) Increased brain lactate is central to the development of brain edema in rats with chronic liver disease. J Hepatol 60:554–560. doi:10.1016/j.jhep.2013.10.011

Bosoi, C. R., & Rose, C. F. (2014). Elevated cerebral lactate: Implications in the pathogenesis of hepatic encephalopathy. *Metabolic brain disease*, *29*(4), 919–925. https://doi.org/10.1007/s11011-014-9573-9

Butterworth RF (2007) Neuronal cell death in hepatic encephalopathy. Metab Brain Dis 22:309–320. doi:10.1007/s11011-007-9072-3

Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at ammonia. Metab Brain Dis. 2002; 17:221–227. [PubMed: 12602499]

Calvert LD, Shelley R, Singh SJ et al (2008) Dichloroacetate enhances performance and reduces blood lactate during maximal cycle exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 177:1090–1094. doi:10.1164/rccm.200707-1032OC

Canevari L, Abramov AY, Duchen MR. Toxicity of amyloid beta peptide: tales of calcium, mitochondria, and oxidative stress. Neurochem Res. 2004; 29:637–650. [PubMed: 15038611]

Cruz NF, Dienel GA. Brain glucose levels in portacaval-shunted rats with chronic, moderate hyperammonemia: implications for determination of local cerebral glucose utilization. J Cereb Blood Flow Metab. 1994; 14:113–124. [PubMed: 8263046]

Cruz NF, Duffy TE. Local cerebral glucose metabolism in rats with chronic portacaval shunts. J Cereb Blood Flow Metab. 1983; 3:311–320. [PubMed: 6874740]

Cudalbu C. (2013). In vivo studies of brain metabolism in animal models of Hepatic Encephalopathy using ¹H Magnetic Resonance Spectroscopy. *Metabolic brain disease*, *28*(2), 167–174. https://doi.org/10.1007/s11011-012-9368-9

Hertz L, Dienel GA (2002) Energy metabolism in the brain. Int Rev Neurobiol 51:1–102

Kala G, Hertz L. Ammonia effects on pyruvate/lactate production in astrocytes interaction with glutamate. Neurochem Int. 2005; 47:4–12. [PubMed: 15890434]

Kimelberg HK, Mongin AA. Swelling-activated release of excitatory amino acids in the brain: relevance for pathophysiology. Contrib Nephrol. 1998; 123:240–257. [PubMed: 9761972]

Kimelberg HK. Current concepts of brain edema. Review of laboratory investigations. J Neurosurg. 1995; 83:1051–1059. [PubMed: 7490620]

Kosenko E, Felipo V, Montoliu C, Grisolia S, Kaminsky Y. Effects of acute hyperammonemia in vivo on oxidative metabolism in nonsynaptic rat brain mitochondria. Metab Brain Dis. 1997; 12:69–82. [PubMed: 9101539]

Krautwald M, Münch G (2010) Advanced glycation end products as biomarkers and gerontotoxins - a basis to explore methylglyoxal- lowering agents for Alzheimer's disease? Exp Gerontol 45:744– 751. doi:10.1016/j.exger.2010.03.001

Lai JC, Cooper AJ. Neurotoxicity of ammonia and fatty acids: differential inhibition of mitochondrial dehydrogenases by ammonia and fatty acyl coenzyme A derivatives. Neurochem Res. 1991; 16:795–803. [PubMed: 1944769]

Mans, A., Hawkins, R., & Biebuyck, J. (1984). Regional cerebral glucose utilization after portacaval shunting. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*, *4*(1), 123–126. https://doi.org/10.1038/jcbfm.1984.17

Norenberg MD, Jayakumar AR, Rama Rao KV. Oxidative stress in the pathogenesis of hepatic encephalopathy. Metab Brain Dis. 2004a; 19:313–329. [PubMed: 15554424]

Norenberg MD, Mozes LW, Gregorios JB, Norenberg LO. Effects of lactic acid on astrocytes in primary culture. J Neuropathol Exp Neurol. 1987; 46:154–166. [PubMed: 3819773]

Norenberg MD, Rao KV. The mitochondrial permeability transition in neurologic disease. Neurochem Int. 2007; 50:983–997. [PubMed: 17397969]

Norenberg MD. Oxidative and nitrosative stress in ammonia neurotoxicity. Hepatology. 2003b; 37:245–248. [PubMed: 12540772]

Norenberg MD. The role of astrocytes in hepatic encephalopathy. Neurochem Pathol. 1987; 6:13–33. [PubMed: 3306480]

Norenberg, MD.; Jayakumar, AR.; Rama Rao, KV.; Panickar, KS. The peripheral benzodiazepine receptor and neurosteroids in the pathogenesis of hepatic encephalopathy and ammonia neurotoxicity. In: Häussinger, D.; KIrcheis, G.; Schliess, F., editors. Hepatic Encephalopathy and Nitrogen Metabolism. Dordtrecht: Springer; 2006. p. 143-160.

Norenberg, MD.; Rama Rao, KV.; Jayakumar, AR. The mitochondrial permeability transition in ammonia neurotoxicity. In: Jones, E.; Meijer, AJ.; Chamuleau, AF., editors. Encephalopathy and Nitrogen Metabolism in Liver Failure. Dordrecht: Kluwer; 2003a. p. 267-286.

Rama Rao, K. V., & Norenberg, M. D. (2012). Brain energy metabolism and mitochondrial dysfunction in acute and chronic hepatic encephalopathy. *Neurochemistry international*, *60*(7), 697–706. https://doi.org/10.1016/j.neuint.2011.09.007

Ratnakumari L, Murthy CR. Activities of pyruvate dehydrogenase, enzymes of citric acid cycle, and aminotransferases in the subcellular fractions of cerebral cortex in normal and hyperammonemic rats. Neurochem Res. 1989; 14:221–228. [PubMed: 2725822]

Ratnakumari L, Murthy CR. In vitro and in vivo effects of ammonia on glucose metabolism in the astrocytes of rat cerebral cortex. Neurosci Lett. 1992; 148:85–88. [PubMed: 1300509]

Ratnakumari L, Murthy CR. Response of rat cerebral glycolytic enzymes to hyperammonemic states. Neurosci Lett. 1993; 161:37–40. [PubMed: 8255543]

Ratnakumari L, Qureshi IA, Butterworth RF. Effect of L-carnitine on cerebral and hepatic energy metabolites in congenitally hyperammonemic sparse-fur mice and its role during benzoate therapy. Metabolism. 1993; 42:1039–1046. [PubMed: 8102193]

Ratnakumari L, Qureshi IA, Butterworth RF. Effects of congenital hyperammonemia on the cerebral and hepatic levels of the intermediates of energy metabolism in spf mice. Biochem Biophys Res Commun. 1992; 184:746–751. [PubMed: 1575747]

Rose C, Ytrebo LM, Davies NA, Sen S, Nedredal GI, Belanger M, Revhaug A, Jalan R. Association of reduced extracellular brain ammonia, lactate, and intracranial pressure in pigs with acute liver failure. Hepatology. 2007; 46:1883–1892. [PubMed: 17705298]

Rose C. Effect of ammonia on astrocytic glutamate uptake/release mechanisms. J Neurochem. 2006; 97(Suppl 1):11–15. [PubMed: 16635245]

Rose C. F. (2010). Increase brain lactate in hepatic encephalopathy: cause or consequence?. *Neurochemistry international*, *57*(4), 389–394. https://doi.org/10.1016/j.neuint.2010.06.012

Schurr A (2006) Lactate: the ultimate cerebral oxidative energy substrate? J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 26:142–152. doi:10.1038/sj.jcbfm.9600174

Staub F, Baethmann A, Peters J et al (1990) Effects of lactacidosis on glial cell volume and viability. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 10:866–876

Tofteng F, Jorgensen L, Hansen BA et al (2002) Cerebral microdialysis in patients with fulminant hepatic failure. Hepatol Baltim Md 36: 1333–1340. doi:10.1053/jhep.2002.36944

Tofteng F, Larsen FS. Management of patients with fulminant hepatic failure and brain edema. Metab Brain Dis. 2004; 19:207–214. [PubMed: 15554416]

Tofteng F, Larsen FS. Monitoring extracellular concentrations of lactate, glutamate, and glycerol by in vivo microdialysis in the brain during liver transplantation in acute liver failure. Liver Transpl. 2002; 8:302–305. [PubMed: 11910577]

Zwingmann C (2007) Nuclear magnetic resonance studies of energy metabolism and glutamine shunt in hepatic encephalopathy and hyperammonemia. J Neurosci Res 85:3429–3442. doi:10.1002/jnr. 21445

Zwingmann C, Chatauret N, Leibfritz D, Butterworth RF (2003) Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [H-C] nuclear magnetic resonance study. Hepatol Baltim Md 37:420–428. doi:10.1053/jhep.2003.50052

Zwingmann C, Chatauret N, Leibfritz D, Butterworth RF. Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [H-C] nuclear magnetic resonance study. Hepatology. 2003a; 37:420–428. [PubMed: 12540793]

Zwingmann C. The anaplerotic flux and ammonia detoxification in hepatic encephalopathy. Metab Brain Dis. 2007; 22:235–249. [PubMed: 17823857]