ELEVATED CEREBRAL LACTATE: IMPLICATIONS IN THE PATHOGENESIS OF HEPATIC ENCEPHALOPATHY

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Abbreviations: HE, hepatic encephalopathy; MG, methylglyoxal; LDH, lactate dehydrogenase; TCA, tricarboxylic acid cycle; ANLS, astrocyte-neuron lactate shuttle; BBB, blood-brain barrier; MCT, monocarboxylate transporter; ALF, acute liver failure; CLD, chronic liver disease; DCA, dichloroacetate

ABSTRACT

Hepatic encephalopathy (HE), a complex neuropsychiatric syndrome, is a frequent complication of liver failure/disease.

Increased concentrations of lactate are commonly observed in HE patients, in the systemic circulation, but also in the brain.

Traditionally, increased cerebral lactate is considered a marker of energy failure/impairment however alterations in lactate homeostasis may also lead to a rise in brain lactate and result in neuronal dysfunction. The latter may involve the development of brain edema. This review will target the significance of increased cerebral lactate in the pathogenesis of HE.

INTRODUCTION

Lactic acid (CH_3-CH(OH)-COOH) is a carboxylic acid which, in solution, can donate a proton from its carboxyl group, forming the lactate ion (CH_3-CH(OH)-COO$^-$). Lactic acid has two optical isomers: D-lactic acid and its mirror image, L-lactic acid.

D-lactate is an end-product formed via the glyoxalase system following glutathione-dependent detoxification of methylglyoxal, a highly reactive dicarbonyl compound mainly formed as a by-product of glycolysis. Methylglyoxal is a major precursor of advanced glycation end products, pathogenic factors involved in aging, neurodegenerative disorders and complications of diabetes (Krautwald and Münch 2010). Therefore, D-lactate levels are used as an indicator reflecting activity of the glyoxalase system. In addition, an increase in D-lactate can lead to acidosis as observed in short bowel syndrome or following injections of propylene glycol (a vehicle used for many intravenous medications) (Zosel et al. 2010). It is also believed to play a role in diabetic ketoacidosis (Bo et al. 2013). D-lactate is poorly metabolized in mammalian cells since D-lactate dehydrogenase is solely expressed in mitochondria and has a lower affinity for D-lactate compared to L-lactate and its respective dehydrogenase (found in mitochondria and cytosol) (Bélanger et al. 2011). Overall, levels of D-lactate are significantly lower in comparison to L-lactate and its implication in various diseases is poorly described.

L-lactate[1], the primary focus of this review, is produced in every cell from pyruvate via a reversible reaction catalyzed by the enzyme LDH[2], which involves the oxidation of NADH to NAD$^+$ (Figure 1A). Glucose-derived pyruvate (via glycolysis) is a substrate of the tricarboxylic acid (TCA) cycle, the metabolic hub of the cell and final common pathway for the aerobic oxidation of fuel molecules. The conversion of pyruvate to lactate is an active pathway occurring primarily in muscle during anaerobic situations (such as during exercise or hypoxia) which regenerates NAD$^+$ needed to sustain the glycolytic pathway. Muscle-derived lactate is metabolized by the liver where it is converted to glucose and used to fuel all organ, including the muscle (Cori cycle) (Woll and Record 1979) (Figure 1B).

[1]Throughout the text, "lactate" will represent L-lactate.
[2]Throughout the text, "LDH" will represent L-LDH.

Traditionally, glucose is considered the only molecule to fuel the brain; however, new evidence demonstrates that lactate, capable of generating energy (ATP), is a preferred oxidative energy substrate over glucose by neurons (as reviewed by (Pellerin and Magistretti 2012)). The "astrocyte-neuron lactate shuttle" (ANLS) states lactate is primary produced by

astrocytes, is released extracellularly and taken up by neurons where it is metabolized and used to fuel the TCA cycle (Schurr 2006; Pellerin et al. 2007). The astrocytes play a major role in regulating the blood-brain barrier (BBB) function as astrocytic end feet wrap around cerebral capillaries; therefore astrocytes are the first cells in the brain exposed to blood-derived glucose. Lactate transporters (monocarboxylate transporters, MCT) are expressed on both astrocytes and neurons. Neuronal MCT2 has a higher affinity than the isoforms MCT1 and MCT4 found in astrocytes (Pierre and Pellerin 2005). LDH also has neuronal and astrocytic isoforms. LDH1 located in neurons has a higher affinity for lactate than the astrocytic LDH5 (Bittar et al. 1996). Therefore, the localization and the dissimilar affinities for lactate of the different isoforms of LDH and MCT in neurons and astrocytes proves that neurons are better equipped to capture and use lactate than astrocytes, therefore sustaining the existence of the ANLS.

LACTATE AND LIVER FAILURE/DISEASE

Liver disease is an important cause of morbidity and mortality associated with a poor quality of life and a high economic burden (Kim et al. 2002). Impaired liver function arises following acute liver failure (ALF) or chronic liver disease (CLD). ALF, a rapid hepatic necrosis in a previously healthy liver, results in severe deterioration of the clinical status and the apparition of jaundice, encephalopathy and coagulopathy. CLD is a long-term progressive loss of hepatic function leading to cirrhosis which is characterized histologically by fibrosis and regenerative nodules. ALF and CLD consequently lead to numerous metabolic disturbances and to an increase in circulating toxins affecting distant organs including the brain.

Hepatic encephalopathy (HE) is a major complication of both ALF and CLD which includes a large spectrum of neurological symptoms, ranging from mild attention, memory and psychomotor disturbances to extrapyramidal symptoms, tremor, ataxia, stupor and coma (Hartmann et al. 2000; Bajaj et al. 2007). An important entity of both ALF and CLD is the presence of brain edema (Rose et al. 2007; Cauli et al. 2011; Bosoi et al. 2014) with intracranial hypertension leading to 25% mortality in ALF patients (Lee 1993).

HYPERLACTATEMIA IN LIVER FAILURE/DISEASE

Hyperlactataemia has been described in various animal models of ALF (Chatauret et al. 2003; Rose et al. 2007) and has been established as a prognostic marker in patients with ALF (Bernal et al. 2002). In CLD, blood lactate levels increase with the severity of cirrhosis (Jeppesen et al. 2013) and are associated with mortality in severe patients (Zauner et al. 2000; Tas et al. 2012). Several mechanisms are implicated in the onset of hyperlactatemia during ALF/CLD: (i) decreased hepatic lactate

metabolism due to hepatocyte loss (i.e interrupted Cori cycle) (Woll and Record 1979; Levraut et al. 1998), (ii) increased lactate release from necrotic hepatocytes (Clemmesen et al. 2000); or (iii) increased extra-hepatic lactate production following multi-organ-failure (Bernal et al. 2002).

SOURCE OF INCREASED LACTATE IN BRAIN IN LIVER FAILURE/DISEASE

Increased brain lactate is commonly observed in HE. In ALF, it has been evidenced by cerebral microdialysis studies in patients (Tofteng et al. 2002; Bjerring et al. 2010) as well as in animal models (Chatauret et al. 2003; Rose et al. 2007; Chavarria et al. 2010). Increased cerebral lactate is strongly correlated with an increase in intracranial pressure (Tofteng et al. 2002; Rose et al. 2007; Bjerring et al. 2008). In CLD, only one clinical study (16 cirrhotic patients) showed an increase in brain lactate (cerebrospinal fluid) (Yao et al. 1987). However, recently our group demonstrated an increase in cerebral lactate in cirrhotic rats was found to play a major role in the pathogenesis of brain edema (Bosoi et al. 2014). Although increased plasma lactate has been evidenced in ALF and CLD patients, in the context of HE, it is unresolved whether systemic lactate is a source for increased cerebral lactate. Even though the BBB, which strictly controls the flow of molecules into the brain, has been shown to express MCT1 on cerebral endothelial cells (Pierre and Pellerin 2005), lactate has been shown not to easily cross an intact BBB (Hertz and Dienel 2002). Clearly, a breakdown of the BBB would facilitate the entry of lactate into the brain which has been evidenced in animals models of ALF: extravasation into the brain of Evans Blue and [^{14}C] alpha-aminoisobutyric acid as well as modifications in the expression of BBB tight junction proteins have been observed in ALF (Yamamoto and Nguyen 2006; Sawara et al. 2009; Chen et al. 2009; Cauli et al. 2011). However, in CLD, the BBB seems to remain intact (Wright et al. 2007; Bosoi et al. 2012). Nevertheless, studies involving animal models of ALF and CLD and using nuclear magnetic resonance (NMR) and ^{13}C-glucose, showed an increase in local production of cerebral lactate (Zwingmann et al. 2003; Bosoi et al. 2014). 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). This is supported by studies showing HE induced by acute ammonia infusion or by ALF does not lead to a decrease in ATP (Lin and Raabe 1985; Fitzpatrick et al. 1989; Mans et al. 1994). However, increased lactate represents more than just a marker reflecting metabolic impairment as elevated levels of brain lactate can also lead to lactic acidosis which can cause adverse cellular effects (Kaila and Ransom 1998). Therefore, an increase in cerebral lactate may be a marker of energy impairment which consequently causes neurological impairment or may directly cause cerebral dysfunction and HE.

INCREASED CEREBRAL LACTATE - ALTERED HOMEOSTASIS?

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 (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. Total brain (astrocyte and neuronal) LDH activity was increased in pigs with ALF induced by hepatic devascularisation. However the specific activity of each LDH isoform was investigated. In anycase, the LDH activity increase persisted following treatment with molecular adsorbent recirculation system in spite of a significant reduction in extracellular cerebral lactate levels (Rose et al. 2007), suggesting a higher need for lactate is required during conditions of HE. However, non-treated animals are unable to consume the increased lactate leading to increased extracellular levels which diminish following treatment. The role of each LDH isoform (astrocytic and neuronal) as well as expression of specific MCTs remains unknown and alterations in ANLS merits investigation in the pathogenesis of HE.

LACTATE AND NEURONAL DEATH

Increased cerebral lactate has been described in numerous neurological diseases like ischemia/infarction but also cerebral tumors, acute seizures, cerebral infectious and inflammatory diseases (abscesses, progressive multifocal leukoencephalopathy, acute disseminated encephalomyelitis, encephalitis), multiple sclerosis, metabolic disorders affecting lipid, carbohydrate, amino acid metabolism or the mitochondria (for review see (Shih et al. 2004)). In the majority of these conditions, neuronal death is frequently observed (Gorman 2008; Languren et al. 2013; Baron et al. 2014).

Given that HE is a metabolic syndrome, it is defined as "reversible" following the treatment of the diseased liver or following a liver transplantation. Therefore, for many decades, there has been very little reason to speculate neuronal cell death occurs in HE. However, with recent observations demonstrating the existence of persisting neurological complications following liver transplantation (Ciancio et al. 2002; Amodio et al. 2007; Sotil et al. 2009; Atluri et al. 2010), the conception of neuronal cell death in HE deserves to be be revisited. In addition, there is some evidence depicting a decrease in ATP is associated with severe HE (Hindfelt et al. 1977), a finding which supports the observations that severe HE (or episodes of

severe HE) pre-liver transplantation significantly impact neurological outcome following liver transplantation (Sotil et al. 2009). Furthermore, as many neurodegenerative diseases are associated with increased brain lactate, this provides further reasoning to pursue the role of neuronal cell death in HE. It is possible, neuronal cell death may only occur under certain liver-induced pathological conditions, including the etiological cause of the disease (Butterworth et al. 1993; Butterworth 2007) or severity of HE (Hindfelt et al. 1977; Therrien et al. 1997). This is an important field of research which merits to be thoroughly investigated.

AMMONIA AND LACTATE RELATIONSHIP

Ammonia has long been considered the main factor involved in the pathogenesis of HE. Ammonia has been demonstrated to increase glycolysis by stimulating the enzyme phosphofructokinase (Lowry and Passonneau 1966), but has also shown to reduce α-ketoglutarate dehydrogenase activity, the rate-limiting enzyme of the TCA cycle (Lai and Cooper 1986). Therefore ammonia toxicity affects energy metabolism and subsequently leads to an increase in brain lactate (Bosman et al. 1990). In fact, acute ammonia injection in normal and portacaval shunted rats led to an increase in brain lactate (Fitzpatrick et al. 1989; Therrien et al. 1997). Moreover, NMR studies evidenced lactate synthesis is dependent on the concentration of ammonia (Zwingmann et al. 2003; Bosoi et al. 2014) and various therapeutic interventions aimed at reducing ammonia such as hypothermia, albumin dialysis, AST-120 (spherical carbon adsorbent) and L-ornithine L-aspartate, have led to a significant reduction in cerebral lactate levels (Vogels et al. 1997; Chatauret et al. 2003; Rose et al. 2007; Bosoi et al. 2014). Two particular studies involving; (i) pigs with ALF (induced by liver devascularisation) and (ii) rats with CLD (induced following bile-duct ligation) demonstrated strong correlations between cerebral ammonia and lactate levels (Figure 2, (Rose et al. 2007; Bosoi et al. 2014)).

Since the direct effects of ammonia toxicity can lead to numerous pathological consequences such as impaired mRNA and protein expression, calcium signaling or inducing oxidative stress (Rose, 2005; Perazzo 2012), altered protein structure and function may ensue (Stadtman and Levine 2000). To this regard, whether increased ammonia affects lactate homeostasis by modulating lactate transporters or enzymes remains to be elucidated in the future.

ROLE OF LACTATE IN BRAIN EDEMA (ALF AND CLD)

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). Lactate is known to induce astrocyte swelling *in vitro* (Staub et al. 1990) and is associated with the development of brain edema in animal models of ALF (Zwingmann et al. 2003; Chatauret et al. 2003; Sen et al. 2006; Chavarria et al. 2010). Furthermore, in patients with ALF, an increase in extracellular brain lactate was found to correlate with increased intracranial pressure (Tofteng et al. 2002). In addition to lactate playing a major role in the development of brain edema in ALF, we demonstrated that in CLD, increased cerebral lactate also induces brain edema in bile duct ligated rats (Bosoi et al. 2014). Overall, the mechanisms by which lactate induces brain edema in the pathogenesis of HE remain unknown. However, it has been speculated that alterations in lactate homeostasis can lead to lactate-induced osmotic changes and hence cell swelling (Preuss 2012).

TREATMENTS FOR HE: TARGETING LACTATE?

Recently, our group tested the effect of dichloroacetate (DCA) (lactate synthesis inhibitor) on the development of brain edema in bile-duct ligated rats and we found a reduction in cerebral lactate resulted in a decrease in brain edema (Bosoi et al. 2014). DCA treatment did not have an effect on degree of hyperammonemia or on hepatic function. This concludes lactate (possibly as a result from ammonia toxicity) plays an important role in the development of brain edema. DCA reduces lactate synthesis by inhibiting PDH kinase (which normally phosphorylates and inactivates PDH) activity. In turn, pyruvate entry into the TCA cycle is increased and less lactate is generated (Figure 3, (Stacpoole et al. 1998)). DCA has been successfully used in patients for the treatment of various tumors as a metabolic modulator, since cancer cells have a high rate of glycolysis followed by lactic acid fermentation in the cytosol (Kumar et al. 2013). DCA has also been shown beneficial in other diseases such as congenital lactic acidosis (Abdelmalak et al. 2013) and chronic obstructive pulmonary disease (Calvert et al. 2008); in these conditions it proved to be safe following long-term administration with no adverse reactions. Therefore, in addition to investigating into novel ammonia lowering strategies for the treatment of HE (Rose 2012), innovative approaches to reduce lactate is a therapeutic avenue which deserves to be further studied. DCA is safe and effective in attenuating increased cerebral lactate and therefore merits to be tested for the treatment of HE in patients with either ALF or CLD.

CONCLUSIONS

Cerebral lactate is commonly increased in patients with HE in both the context of ALF or CLD. An increase in brain lactate may reflect energy failure/impairment and/or alterations in lactate homeostasis. In addition, elevated levels of lactate may induce cellular dysfunction/death through lactic acidosis. In all cases, disturbances in ANLS (and hence alterations in lactate homeostasis) may be involved which remains poorly understood in the pathogenesis of HE. Increased cerebral lactate is associated with various neurodegenerative diseases and therefore neuronal cell death in HE merits to be revisited. The strong correlation between ammonia and lactate supports ammonia-lowering strategies remain at the forefront for the treatment of HE however directly attenuating increased lactate represents an therapeutic option which merits to be further investigated in patients with HE.

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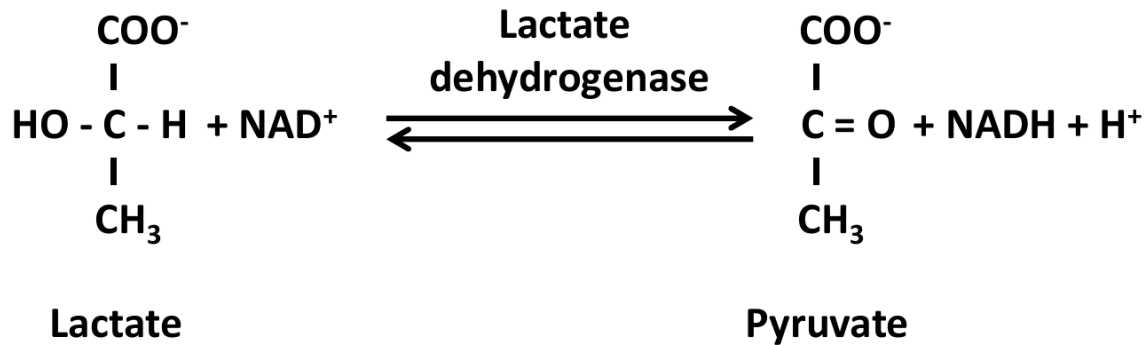
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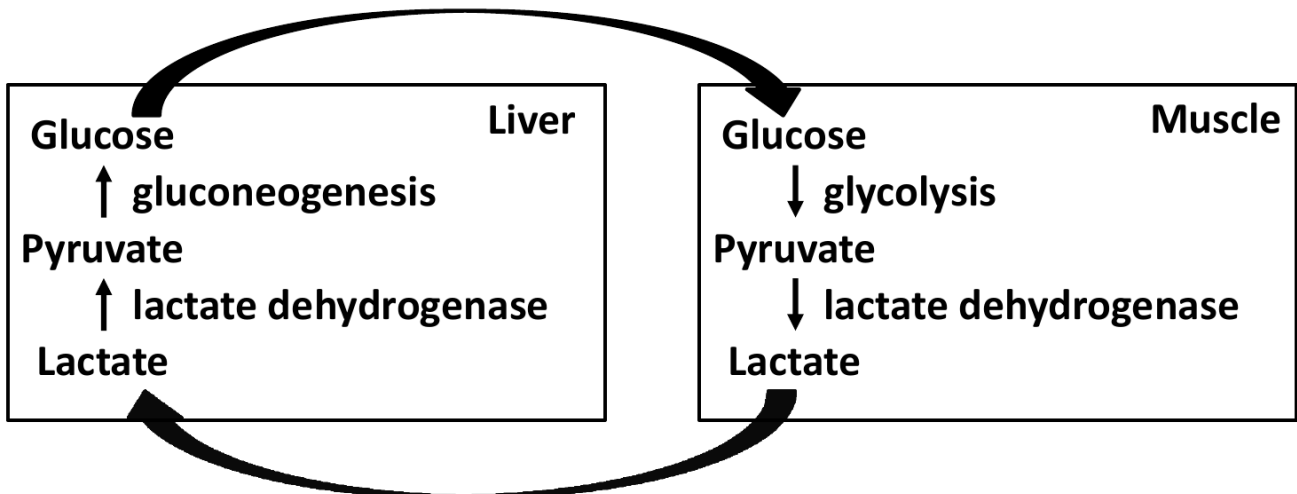
FIGURE LEGENDS

A

$$
\begin{array}{ccc}
\text{COO}^- & & \text{COO}^- \\
| & & | \\
\text{HO - C - H} \;+\; \text{NAD}^+ & \underset{\xleftarrow{\hspace{2cm}}}{\xrightarrow{\hspace{2cm}}} & \text{C = O} \;+\; \text{NADH} + \text{H}^+ \\
| & & | \\
\text{CH}_3 & & \text{CH}_3 \\
\\
\text{Lactate} & & \text{Pyruvate}
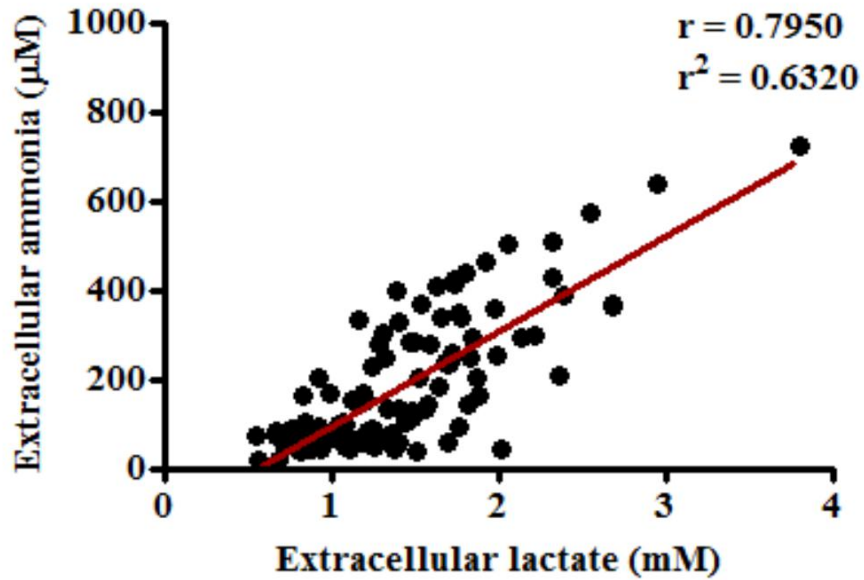\end{array}
$$

Lactate dehydrogenase

B

Figure 1: A) The reversible reaction from lactate to pyruvate catalyzed by lactate dehydrogenase. B) The Cori cycle: the liver recycles the lactate produced by the muscle into glucose which fuels the organs, including the muscle.

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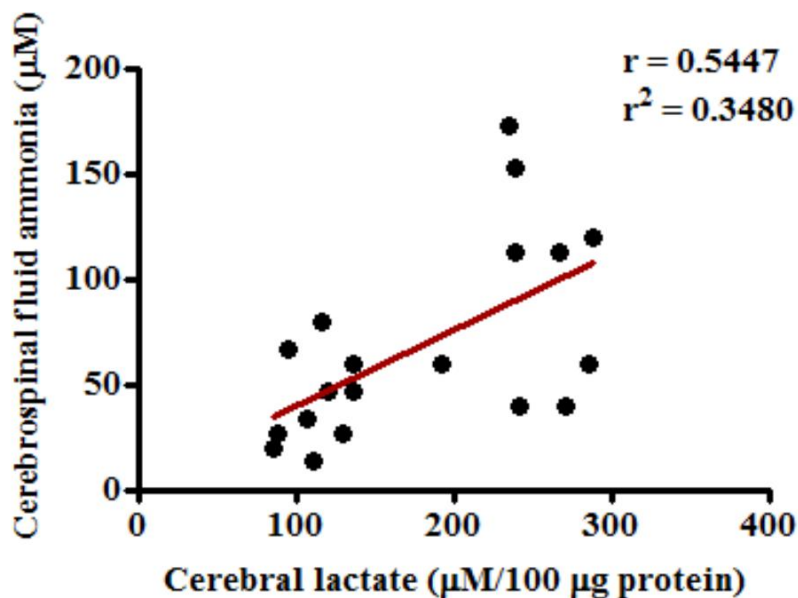
A

B

Figure 2: Correlations between cerebral ammonia and lactate during acute liver failure and chronic liver disease. A) Correlation between cerebral extracellular ammonia and lactate (obtained by microdialysis) in pigs with acute liver failure induced by liver devascularisation. B) Correlation between cerebrospinal fluid ammonia and cerebral tissue lactate in rats with chronic liver disease induced by bile-duct ligation (after Rose et al. 2007; Bosoi et al. 2014).
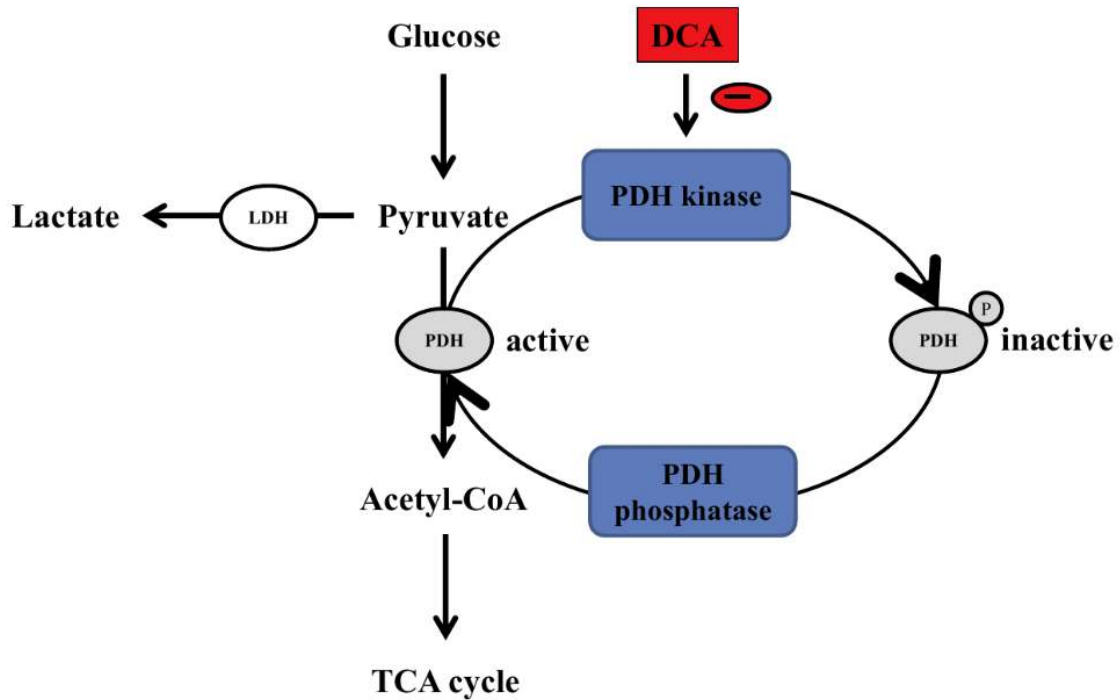
Figure 3: Mechanism of action of dichloroacetate (DCA). Normally, pyruvate dehydrogenase (PDH) activity is regulated by a PDH kinase. This inhibits PDH activity by phosphorylating it (P). As a consequence, pyruvate flux into the tricarboxylic (TCA) cycle is maintained at a basal level and pyruvate is available for lactate dehydrogenase (LDH) which converts it into lactate, allowing lactate synthesis. DCA inhibits the PDH-kinase, therefore PDH is activated and the pyruvate flux into the TCA cycle increases, shifting the LDH toward pyruvate production thus decreasing lactate synthesis.