Lactate and Traumatic Brain Injury

By

Nicole Mallory

A Master's Paper
Submitted in Partial Fulfillment of
the Requirements for the Degree of

Master of Science in Clinical Exercise Physiology

________________________________________
Dr. Joseph O’Kroy

________________________________________
Date

University of Wisconsin – River Falls

2015
# Table of Contents

Introduction .................................................. 3  
Traumatic Brain Injury .................................... 4 
Treatment for Traumatic Brain Injuries ............... 5 
Astrocyte-Neuron Lactate Shuttle ...................... 6 
Lactate and the Benefits of Lactate ................. 7 
The Brain and Lactate ..................................... 9 
Traumatic Brain Injury and Lactate ................ 10 
Current and Future Research ......................... 13 
Conclusions ............................................... 16 
References ............................................... 17
Introduction

For decades, glucose has been thought to be the biggest factor affecting the human brain, because it is the main energy substrate. When the body is in a state of energy depletion the supply of glucose may be limited, which in turn can lead to a critically reduced level of cerebral extracellular glucose (Bouzat, Sala, Suys, Zerlauth, Marques-Vidal, Feihl, Bloch, Messerer, Levivier, Meuli, Magistretti, & Oddo, 2014). Cureton, Kwan, Dozier, Sadjadi, Pal, and Victorino (2010) and Smith, Pernet, Hallett, Bingham, Marsden, and Amiel (2003) suggest that glucose is not the only important energy substrate for energy metabolism and that lactate is just as crucial. However, some researchers consider that lactate is not a crucial energy substrate to the brain for energy metabolism due to the impression that lactate is just a waste product from glycolysis (Bouzat & Oddo, 2014; Dienel, 2014; Jalloh, Helmy, Shannon, Gallagher, Menon, Carpenter, & Hutchinson, 2013; Rice, Zsoldos, Chen, Wilson, Alessandri, Hamm, & Bullock, 2002) or due to lactate being impermeable to the blood-brain barrier, suggesting that it is a useless energy substrate (Schurr, Payne, Miller, & Rigor, 1997). Conversely, in the past decade research has been completed that suggest “neurons can carry out synaptic functions with only lactate as the available source” (Rice et al., 2002; Schurr et al., 1997; Schurr, 1998, Schurr, 1999). This concept helps to propose that lactate is an acceptable fuel for neurons.

Lactate has started becoming just as important, if not more important than glucose in regards to traumatic brain injuries. In individuals with traumatic brain
injury, lactate levels in extracellular fluid begin to increase whereas glucose levels decrease. This poses the idea that lactate may be preferentially produced by injured tissue (Rice et al., 2002).

**Traumatic Brain Injury**

Traumatic brain injuries are a major health problem and is a leading cause of mortality and disability, (Maas, Stocchetti, & Bullock, 2008) this is partially due to there being no cure for traumatic brain injury (Rice et al., 2002). Every year more than 50,000 individuals die due to traumatic brain injury, and an additional 70,000-90,000 individuals are permanently disabled (Rice et al., 2002; Thurman & Guerrero, 1999). The World Health Organization predicts that by the year 2020 traffic deaths will be the third greatest cause of injury, and traumatic brain injury mainly occurs because of traffic accidents (Maas et al., 2008). Thus, while there is no cure for traumatic brain injuries, it is important to reduce the damage that can occur in the brain as a result of a traumatic injury (Rice et al., 2002).

A traumatic brain injury results from an outside force causing tissue damage and from that damage, many different cellular processes occur following the initial force that caused the injury. Even in severe cases of traumatic brain injury, the damage that is caused is not necessarily evident on a CT scan of the brain, suggesting that there is a great impact on the neurological and cellular function of the brain (Carpenter, Jalloh, and Hutchinson, 2015). There are two classifications of brain injury, primary damage and secondary damage. Both primary and secondary damage include the shearing of white-matter tracts, focal contusions, intracerebral
and extra cerebral hematomas, and diffused swelling (Fillenz, 2005). Secondary damage is more severe than primary damage and the mechanisms can last and develop progressively. Primary damage is physical damage to the tissues and vessels (Haddad & Arabi, 2012).

Secondary damage includes the events that occur after the initial brain injury involving the combination of cerebral blood flow, oxygen, and energy supply (Bouzat & Oddo, 2014). The response to brain damage occurs within a few days, but within a few hours following a brain injury cytokines are released from microgila and astrocytes in white matter (Fillenz, 2005). When microgila and astrocytes are released, the blood brain barrier opens and the initial activation of cell death occurs (Maas et al., 2008). Rice et al. (2002) suggest that when there is damage to the cell membrane and/or impaired mitochondrial function apoptosis and energy metabolism failure may occur (Lama, Auer, Tyson, Gallagher, Tomanek and Sutherland, 2014). Secondary damage to the brain can possibly be prevented if the neurons have access to lactate. When given lactate, injured brain cells show less calcium overload, which is a precursor to apoptosis. Chen, Qian, Rice, Zhu, Di, & Bullock (2000) and their team of researchers reported that when lactate is administered intravenously the injured brain takes it up; leading to a preservation of the brains extracellular glucose levels post injury (Chen et al., 2007).

Treatment for Traumatic Brain Injuries

For many physicians treating patients with a traumatic brain injury, mannitol infusion was the preliminary treatment to reduce the amount of pressure in the
brain after an injury. Ichai, Armando, Orban, Berthier, Rami, Samat-Long, Grimaud and Leverve (2008) researched the differences that both sodium lactate and mannitol infusion had on intracranial pressure in patients with a traumatic brain injury. In this study Ichai et al. (2008) had a total of thirty-four patients, and within that eight of the seventeen patients in the mannitol group had rescue therapy with lactate, whereas in the lactate group five of the seventeen patients received rescue therapy with mannitol. Therefore indicating that the number of treatment episodes that needed rescue therapy was higher in the patients that initially received mannitol than it was in the patients that initially received lactate. Their results indicated that there was a more definite decrease in intracranial pressure in the patients that received the lactate treatment alone rather than the patients that received only mannitol or the mannitol with rescue therapy of lactate. Not only did Ichai et al. (2008) find that the treatment with the lactate solution was more effective immediately in reducing intracranial pressure, they also followed up with the patients after a year and stated that the patients treated with lactate infusion alone had a more improved neurological status than the patients that were treated with mannitol infusion.

Astrocyte-Neuron Lactate Shuttle

The first researchers to discover that astrocytes could uptake glucose and in turn convert that into lactate were Pellerin and Magistretti (1994). This process, which is termed the astrocyte-neuron lactate shuttle was one of the first processes that challenged the idea that lactate was not just a waste product. Once lactate is
produced, it is transported to various neurons to be used in the tricarboxylic cycle. The astrocyte-neuron lactate shuttle suggests neurons that are activated use lactate that is provided by astrocytes in the body (Fillenz, 2005; Jalloh et al., 2013; Smith et al., 2003; Tanaka, Nakamura, Mizokawa, Matsumura, Matsumura, Murata, Shigematsu, Kageyama, Ochi, & Watanabe, 2004). The astrocyte-neuron lactate shuttle is a controversial topic, due to the fact that the studies conducted look into in vitro experiments, which are done in the laboratory, and not in vivo, which is in the body, whether it is in animals or humans (Smith et al., 2003). It is hypothesized that there is an increase in lactate due to the uptake of glutamate (Fillenz, 2005). Lactate that is produced in astrocytes gets transported into neurons, and this transportation helps with neuron function when the brain is under glucose deprivation (Tanaka et al., 2004).

Lactate and the Benefits of Lactate

Lactate is released during anaerobic metabolism; and cells in the brain can use lactate as another energy source (Cureton et al., 2010; Jalloh et al., 2013). Lactate is used as a signaling function in the brain for both hypoperfusion and shock. Elevations in lactate could be due to ischemia, hypoxia, or medications an individual is taking (Bouzat & Oddo, 2014; Cureton et al., 2010).

Lactate can signal to increase the blood flow and fuel that is being delivered to the brain. It has been thought that lactate is unable to cross the blood brain barrier, deeming it useless as an energy substrate (Schurr et al., 1997). However, many researchers, including Chen et al. (2000), Schurr et al. (1997), Smith et al.
(2003) have discovered that the impermeability of lactate through the blood brain barrier, and that the majority of lactate that an adult brain consumed was produced by cerebral glycolysis during oxygen deprivation. Previous studies have indicated that after a traumatic brain injury lactate may cross the blood brain barrier in increased levels (Chen et al., 2000) and that lactate can cross the blood brain barrier with a permeability of nearly 50% that of glucose (Smith et al., 2003). It has also been discovered that the production and accumulation of lactate occurs not only when the brain is lacking oxygen, but also under cerebral stimulation under normal oxygen conditions. Suggesting that the brain is responsible for producing lactate alone, and without the assistance of the lactate that crosses through the blood brain barrier (Schurr et al., 1997).

Brain lactate appears to fuel the recovery of synaptic function (Chen et al., 2000; Phillis, Song, Guyot, & O'Regan, 1999). The discovery that lactate can maintain synaptic function in the brain suggests that lactate acts as a non-glucose fuel in neurons (Tanaka et al., 2004). Studies have shown that lactate causes an increase in vasodilation, which is the widening of blood vessels in the brain (Yamanishi, Katsumura, Kobayashi, & Puro, 2006). As lactate is increasing in the brain lactic acidosis occurs, which is a condition in which tissue in the body has a low pH and there is a build up of lactate. Lactic acidosis accounts for reduced cerebral blood flow during reperfusion due to the swelling of endothelial cells (Phillis et al., 1999).

When the brains' lactate levels are increased the brain is able to take up more of the lactate, potentially using it for energy generation rather than using
glucose. Jalloh et al., (2013) found that there was a "pattern of decline in glucose and a rise in lactate during the course of a week of monitoring" in patients with traumatic brain injury. Additionally, the uptake of lactate post-traumatic brain injury may be crucial for potentially neuroprotective pathways, which use glucose (Jalloh et al., 2013). Carpenter, Jalloh, and Hutchinson (2015) state, “lactate uptake may reflect an adaptive response to the increased energy demands and change in metabolic priorities of the injured brain. The injured brain's capacity to use endogenous lactate as an alternative fuel implies that exogenous lactate may be therapeutic in TBI patients.”

**The Brain & Lactate**

Gallagher, Carpenter, Grice, Howe, Mason, Timofeev, Menon, Kirkpatrick, Pickard, Sutherland, and Hutchinson (2009) along with the findings from Pellerin and Magistretti (1994) suggest that the injured human brain is able to metabolize lactate through the tricarboxylic acid cycle. Gallagher et al. (2009) used microdialysis, a crucial factor for the measurement of endogenous molecules and the monitoring of cerebral metabolism to assist in determining the way that the brain used lactate. Microdialysis is used in a lot of research, and has helped to increase the understanding of brain injuries and the pathophysiology of the brain when an injury occurs. This study was one of the first to “demonstrate that the human brain can utilize lactate as an energy source via the TCA cycle.”
**Traumatic Brain Injury & Lactate**

Studies have evaluated the affect that lactate has on brain tissue in individuals that have sustained a traumatic brain injury, and Adamides, Rosenfeldt, Winter, Pratt, Tippett, Lewis, Bailey, Cooper, and Rosenfeld (2009) reported that the elevation of lactate in the injured brain was found to be the best predictor of intracranial hypertension, which they define as "the cornerstones of severe traumatic brain injury management."

Lactate is released from the brain in an individual with traumatic brain injury due to ischemia, hypoxia, or anaerobic respiration. Following a traumatic brain injury the level of lactate in the blood and cerebrospinal fluid increases (Chen et al., 2000; Cureton et al., 2010). Studies that have researched lactate and the brain have found that there is an increase in brain glucose with reoxygenation, which suggests that lactate was being utilized; therefore allowing glucose to accumulate in the brain (Phillis et al., 1999).

When it comes to trauma in the brain the amount of lactate that is found tends to be elevated even though an individual with traumatic brain injury has sufficient oxygen delivery to their brain (Jalloh et al., 2013). This increase in lactate is common after traumatic brain injury, and Menzel, Doppenberg, Zauner, Soukup, Reinert, and Bullock (1999) suggests that this is due to a shift from aerobic to anaerobic metabolic pathways. They believe this shift is due to the neurons and astrocytes that signal the shift from aerobic to anaerobic to occur (Menzel et al., 1999). Additionally, after an individual sustains a traumatic brain injury they
experience mitochondrial dysfunction, which causes mitochondrial enzymes to fail. When the mitochondrial enzymes fail, Pyruvate dehydrogenase assists in bringing Pyruvate into the tricarboxylic acid cycle, which increases the amount of lactate that is produced (Jalloh et al., 2013). In addition to that, an isoform of lactate dehydrogenase, LDH5, is found in astrocytes and promotes the conversion of pyruvate to lactate (Fillenz, 2005).

Elevated lactate levels return to normal levels after 24 to 36 hours from the initial brain injury. However, lactate levels in the cerebrospinal fluid remain at a higher level, and when this occurs death is more common (Chen et al., 2000; Cureton et al., 2010; De Salles, Muizelaar, & Young, 1987).

In a study done by Cureton et al. (2010) the researchers hypothesized that lactate would be higher in patients that had a more severe traumatic brain injury, and with that, elevated levels of lactate may be neuroprotective. With this study, 555 traumatic brain injury patients were assessed with varying levels of lactate treatment. They found that the mean lactate levels in the mild, moderate, and severe head injury patients increased with the severity of trauma. The probability of survival was 100% in the patients that had received >5mmol/L of lactate. Additionally, they discovered that lactate was neuroprotective, and cognitive improvements were noted.

Menzel et al. (1999) found that during the first day post-traumatic brain injury the PO2 in the brain is lower, and is strongly correlated to high levels of lactate in the brain when compared to successive days.
Phillis et al. (1999) stated that “lactate supplementation reduced the influx of ischemia-evoked amino acid and enhanced EEG recovery” and supplementation using 40mM showed nearly 50% recovery during the period of reperfusion. Therefore, they concluded that there is an association between elevated lactate levels and greater recovery of EEG activity during reperfusion.

In an in vitro study done by Chen et al. (2000) the researchers found that the rats that were given a lactate injection intravenously showed a significant increase in lactate uptake into the injured cortex in correlation with the normal brain, and this peaked between 10-20 minutes after the initial injury. The injured rats had a significantly higher uptake of lactate, which raises speculation to the question whether the blood brain barrier undergoes damage after traumatic brain injury (Chen et al., 2000).

Jalloh et al. (2013) reported that in their study done in vivo found an overall decline in glucose and an increase in lactate over the course of monitoring the patients. When the researchers compared their results with results for healthy brain extracellular physiological ranges they found that at the third day posttraumatic brain injury, the patients’ glucose critically declined resulting in the import of more lactate from the bloodstream. Suggesting that the increase in brain lactate that is seen after traumatic brain injury is indicative of uptake from circulation, and that tissue hypoxia contributes to brain extracellular lactate elevation (Jalloh et al., 2013).
Current and Future Research

Cureton et al. (2010) concluded that neurons could use lactate and release lactate to protect injured neurons to maintain cognitive development. Lactate from the ischemic brain can enhance the lactate that is released by the glial cells, which in turn can protect the injured neurons.

Smith et al. (2003) wanted to find that the healthy human brain would use lactate in preference to glucose. In their research they found that the brain uses the lactate within the brain to some extent over glucose. Their study included eight healthy men, and used FDG, which is an analog of natural glucose, PET scans, MRI scans, and arterial blood samples for both glucose and lactate to measure the uptake of global and regional brain glucose. In addition to infusing the eight men with sodium lactate, as a control, the researchers infused sodium bicarbonate at a separate time. The study revealed that there was no difference in the plasma glucose concentration at baseline and during both infusions, however all showed a decrease in brain glucose uptake, and the concentration of plasma lactate increased significantly (Smith et al., 2003).

Rice et al. (2002) found that there is a clinical relevance to using lactate in individuals with traumatic brain injury, and that lactate could very well represent a therapeutic option after brain injury. They infused lactate into injured animals and found that the injured animals had a significant cognitive ability improvement as compared to injured animals that were infused with a saline solution (Rice et al., 2002).
In the past six years, Dr. George Brooks, a professor at the University of California-Berkeley in conjunction with neurosurgeons at University of California-Los Angeles have been conducting research on brain metabolism after a traumatic brain injury. Brooks wanted to “demonstrate that the lactate shuttle could be used to bypass the blockage of glucose metabolism in the brain”. The initial study was based on tracers that measured the amount of lactate entering and leaving the brain. This initial study included 38 patients that had traumatic brain injury at the University of California-Los Angeles (Phys. Org., 2010). Brooks joined the study and was responsible for adding C13 to lactate, which is an anon-radioactive and stable isotope. The C13 acted as a tracer that allowed the researchers to determine if the lactate molecule produced carbon dioxide (UCLA Newsroom, 2007). The researchers involved with this study using the tracers found that the first 12-14 hours after the individual sustained the injury, the brain preferred lactate. However, it has been difficult for Brooks and the University of California-Los Angeles to find patients to include in further studies because of the restrictions on patients, and the limited amount (n=38) of patients. In order to confirm this, Brooks was hoping to find 20-30 additional people to participate in the study. The overall goal of this research is to create a lactate compound to be formed for treatments in patients with traumatic brain injuries (Phys. Org., 2010; UCLA Newsroom, 2007).

Lactate therapy after traumatic brain injury is still at its newer phases of testing. However, strides to using lactate therapy in a clinical setting are being considered in a clinical trial in Switzerland. A clinical trial of lactate therapy is being
performed by Lausanne University Hospital in Switzerland. The goal of the clinical trial is to examine the effects that sodium lactate infusion has on the brain. This clinical trial began in March 2012 and is due for completion in March 2015 (U.S. National Institutes of Health Clinical Trials, 2012). Bouzat et al. (2014) published information on this clinical trial and thus far 15 patients with severe traumatic brain injury were treated. They used 1000 mmol/L of hypertonic sodium lactate infused continuously over three hours in all patients “at 40mcg/kg/min x 60min followed by 30mcg/kg/min for an additional 120min”. All of the patients in the clinical trial began receiving the sodium lactate treatment 33±16 hours from the initial injury. At six months post treatment nine patients in the study (60%) had favorable outcomes, three patients had poor outcomes, and three patients did not survive (Bouzat et al. 2014).

There are still many unknowns about how lactate impacts the brain after traumatic brain injury, and the unknowns make it difficult for researchers to pinpoint how exactly it will affect the brain. Many researchers state their limitations have been due to the small sample size of individuals with moderate or severe brain injury (Cureton et al., 2010). Additionally, another limitation that researchers found was the lack of neurological status after discharge, because the patients are not followed for a length of time. Thus, the researchers are unable to have accurate data and results to show the strengths of the study. An additional factor that limits the studies on lactate and traumatic brain injury is that many studies are done in vitro, meaning that they are done in a laboratory setting, often through growth in test
tubes or petri dishes. It was not until the past ten years that studies were completed in vivo, in animals, and within the past five years studies have been completed in vivo, in humans.

Conclusions

Researchers have shown the benefits of lactate therapy in animals, and more recently human subjects have also shown benefits of this therapy. Bouzat and Oddo (2014) state, “lactate therapy not only had beneficial cerebral metabolic effects, but also was associated with a significant intracranial pressure reduction. Lactate can protect the neurons at a cellular level, resulting in cognitive improvements (Cureton et al., 2010) lactate is the preferred energy substrate for neuron function during recovery when the brain is deprived of oxygen for a period of time (Schurr et al., 1997). Therefore, there is an importance in pursuing research regarding infusion of lactate into the human brain – especially when it comes to cognitive recovery (Rice et al., 2002).

Within the past year, Brooks and Martin (2014) and Bouzat et al. (2014) have published studies that both show the need for further research, and shows the key role that lactate therapy has in regards to traumatic brain injury recovery. If the brain sustains a traumatic injury and lactate is available to use, the injured brain is more likely to recover than it would be able to without it. An elevated lactate level in the brain is seen in individuals with traumatic brain injury, and is also associated with improvements in neurological function (Cureton et al., 2010).
References


