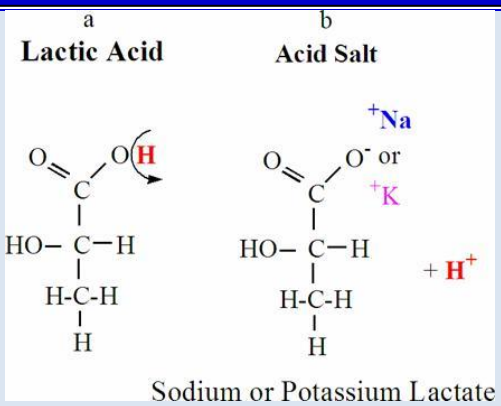
Lactate Efflux From Muscle

As you have now studied, most of the lactate production during exercise occurs in contracting skeletal muscle. While this is true, muscle is not the only tissue that can produce lactate, and a great example of this are blood cells. Blood cells have no mitochondria, and the entirety if energy catabolism is based on glycolytic ATP turnover. However, given that the H^+ buffering of lactate production balances the H^+ release from glycolysis, blood cell energetics does not contribute to systemic acidosis. Thus, while there is a small source of lactate production from blood, and this arguable accounts for most of the resting blood lactate concentration of ~ 1 mmol/L, the exercise-induced increases in blood lactate occur from lactate efflux from muscle. As will be explained in this Topic, this is a rapid process, but unfortunately for cells, a process that has a finite capacity that is below the cellular capacity for peak lactate production.



After lactate is produced in muscle during exercise, lactate can be transported out of the muscle fiber through a specialized transport protein. This protein has been called a **monocarboxylate transporter (MCT)**, as it transports either of pyruvate or lactate (**carboxylates**) one at a time (mono). Molecular biology research has revealed a family of MCT proteins, with the expression of specific types of MCT proteins known to differ between slow vs. fast twitch muscle. Interestingly, research has also identified the presence of a lactate and pyruvate MCT (MCT1) in the inner mitochondrial membrane. There is also a **proton-lactate MCT** within the muscle sacolemma that removes both lactate and a proton from the muscle fiber (Figure 1).

While the presence of the MCT was somewhat obvious given all the prior research on increasing blood lactate accumulation during intense exercise, the finding of the MCT1 protein in mitochondrial membranes is very interesting. This would assist pyruvate conversion to acetyl CoA within the mitochondria, as there would now be two methods for

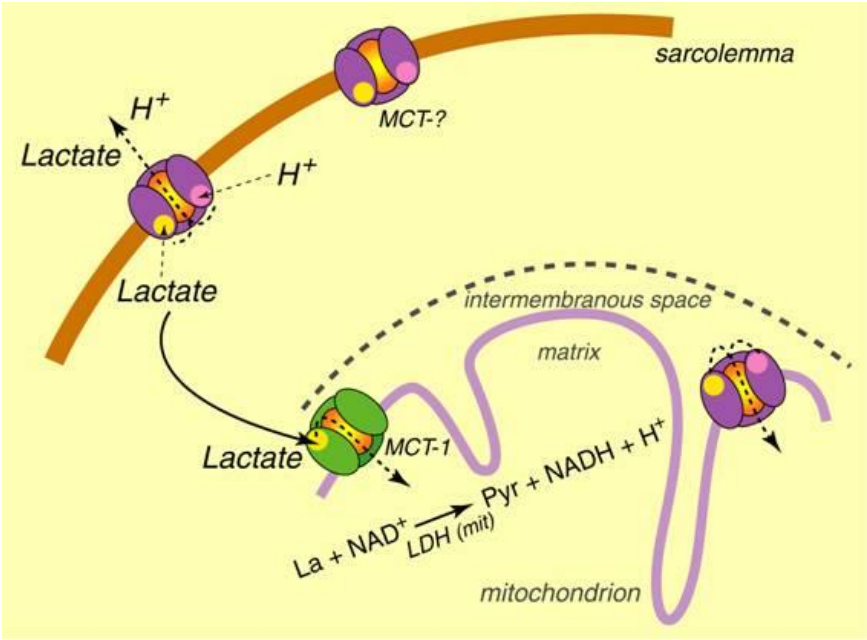


Figure 1. Function of the muscle proton-lactate monocarboxylate transporter.

transferring cytosolic 3 carbon intermediate precursors to pyruvate into the mitochondria. However, it remains unclear how beneficial this added process is by improving mitochondrial respiration, or how it aids in retarding lactate accumulation inside working muscle.

Added research on the MCT family shows that they can be saturated. That is, muscle lactate production can exceed the capacity of the transporter to remove lactate from muscle. This finding is also rather obvious, as decades or prior research has shown muscle lactate accumulation occurs during intense exercise, and continues to despite large increases in blood lactate. Furthermore, research of post-exercise blood lactate shows continued increases in blood lactate during the initial minutes of recovery. This has been interpreted as evidence of continued lactate efflux from muscle caused by the greater concentration of muscle vs. blood lactate.

Benefits of Lactate Efflux From Working Muscle

Metabolic Fuel

There are several explanations for the benefit of muscle and blood lactate accumulation. First of all, muscle lactate can leave the working muscle and be taken up by inactive muscle locally, or in different anatomical regions of the body, where lactate can be used as a pyruvate precursor for mitochondrial respiration (Figure 1). As such, lactate is functioning as a 3 carbon substrate for energy catabolism, and as the lactate dehydrogenase reaction is close to equilibrium, high lactate concentrations can drive the free energy release to favor pyruvate production. This is more likely to occur in resting slow twitch muscle that has the mitochondrial mass to provide sufficient NAD^+ to the cytosol to support this directionality.

Another metabolic benefit of lactate efflux is to fuel kidney and liver gluconeogenesis, as will be discussed in the Topic “Gluconeogenesis” within the Anabolism Section. In this function, lactate can be used to reform glucose, and thereby support blood glucose regulation and spare liver glycogen. The glucose produced from lactate can also be used to synthesize more glycogen in the liver, or after being returned to the blood, support the glucose needs of the working muscle for glycolysis. During the immediate post-exercise recovery, such lactate derived glucose can also be used to assist the replenishment of muscle glycogen. The conversion of lactate to glucose in the liver, and the subsequent release of glucose to the blood has been termed the **Cori cycle**.

Finally, lactate is also a preferred fuel for the myocardium (heart muscle). The reverse direction of the lactate dehydrogenase (LDH) reaction is facilitated by a different LDH **isozyme** than skeletal muscle that has higher catalytic activity for pyruvate production during conditions of low lactate concentrations. Thus, as long as pyruvate concentrations remain low in the myocardium, which they almost always are due to the high mitochondrial density of the myocardium, the bioenergetics of the myocardial LDH reaction favor pyruvate production.

Acid-base Regulation and the Membrane Potential

As lactate acquires a cation to form either sodium lactate or potassium lactate, high rates of muscle lactate production causing high muscle lactate accumulation removes positive charge from the cytosol. However, the strong ion characteristics of lactate prevent all lactate from being protonated. It has been proposed that such a response retards the loss of potassium from working muscle, which can leave through leaky potassium channels. This in turn stabilizes the membrane potential, and may prevent cramp.

Another possible benefit of muscle lactate accumulation concerns **electrochemical neutrality** and its role in determining the final cellular pH. Although more content is given to this issue in the Section on Metabolic Acidosis, you need to understand that the pH of biological solutions is influenced and perhaps largely determined (but not caused!) by charge. This is because pH is a measure of the H^+ concentration or activity, and the H^+ has a +1 charge. To maintain electrochemical neutrality, or for excitable cells the normal membrane potential, the cell needs to match added positive charge with added negative charge. A way to do this when there are protons released from catabolism is to add negative charge, such as lactate accumulation. In addition, the cell can minimize the H^+ contribution to the net positive charge component by better maintaining added positive charge inside the cell. Better sustaining intracellular sodium and potassium will keep H^+ content lower, thus retarding decreases in cellular pH. Such rationale is based on the Stewart approach to acid-base balance. While it remains a theory, and has not received convincing research-based validation, the concept of the forces and energetics governing electrochemical neutrality is without question.

The bottom line here is that there are many known and added potential benefits of muscle lactate production and accumulation. Lactate is really a “good” molecule to muscle function, and we have to remove the myth of fatigue and detriment away from our mind set when studying or discussing lactate metabolism, muscle fatigue, and both muscle and systemic metabolic acidosis.

Glossary Words

monocarboxylate transporter (MCT) is the protein molecule located in the sarcolemma and inner mitochondrial membrane that transports either of pyruvate or lactate across the membrane.

carboxylate is the chemical structure term pertaining to the carboxylic acid (-COOH) functional group.

proton-lactate MCT is the monocarboxylate transporter that is specific to the binding of both lactate and a proton (H^+).

Cori cycle is the 9 reaction cycle within mitochondria that removes carbon dioxide, electrons and protons from acetyl CoA after it is added to oxaloacetate (4 carbons) to form citrate (6 carbons).

isozyme is a molecule that has the same chemical formula but a different chemical structure to another.

electrochemical neutrality refers to the physical chemistry principle based on the forces involved in sustaining charge neutrality within and between cells, as well as the free energy required to oppose it.