Lactate Down-Regulates Hexokinase and 6-Phosphofructo-1-Kinase Activities in Different Tissues from Mouse

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Our previous studies have shown that lactate reduces the affinity of purified 6-phosphofructo-1-kinase (PFK) for its substrates, ATP and fructose-6-phosphate, and inhibits the enzyme by favoring the dissociation of the fully active enzyme tetramers into less active dimers. These effects were dependent on PFK concentration and were not due on changes promoted by lactate on media pH. Furthermore lactate inhibits glucose consumption in intact mouse skeletal muscle, as well as PFK activity measured on muscle homogenates. These results supported the statement that lactate down-regulates the glycolytic flux in skeletal muscle by modulating PFK activity. Here we investigate whether the effects promoted by lactate occur in a more physiologic model and could be extended to other key glycolytic enzyme, hexokinase (HK), in different tissues. We show that pre-incubation in the presence of lactate inhibits (a) PFK and HK activities measured on heart homogenates, (b) HK activity on hepatic and adipose tissues homogenates and (c) PFK activity on skeletal muscle homogenates. Furthermore, the pre-incubation in the presence of lactate prevents insulin effects on PFK activity (skeletal muscle, hepatic, heart and kidney tissues) and HK activity (skeletal muscle). On the other hand, lactate does not affect purified HKI, suggesting that the inhibitions observed occur in other isoform of the enzyme (HKII-IV). In conclusion, our results support evidences that lactate regulates the glycolytic flux through modulating PFK and HK activities in different tissues.

Key words: glycolytic flux, hexokinase, insulin resistance, lactate, phosphofructokinase
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