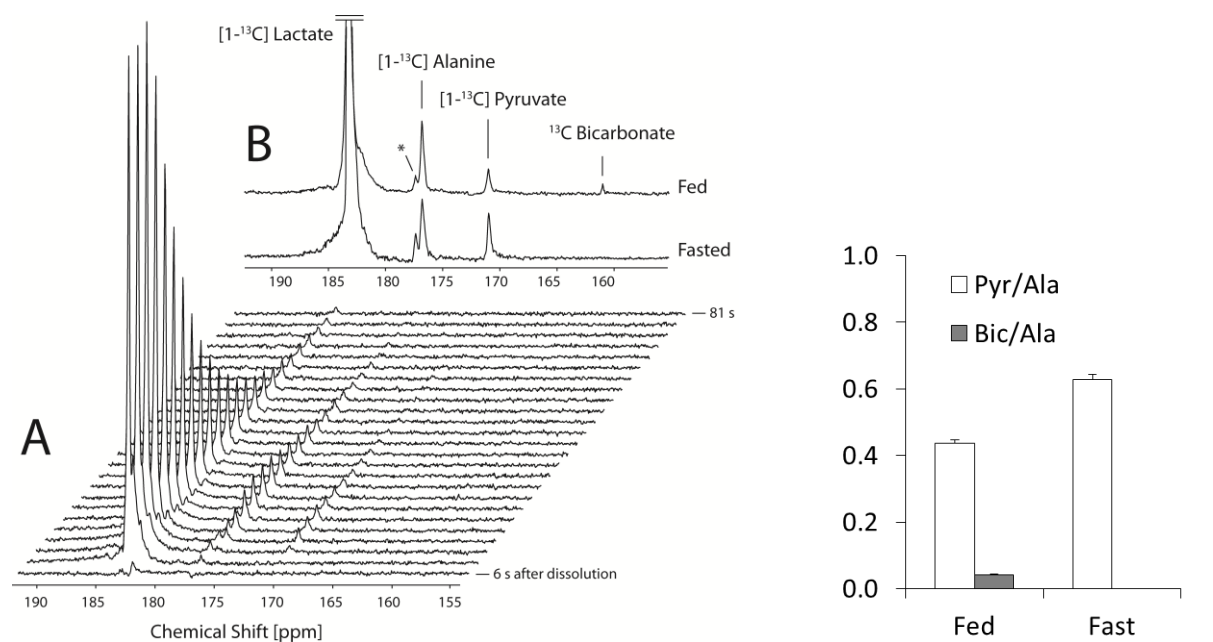


Resting skeletal muscle has a preference for the oxidation of lipids compared to carbohydrates and a shift towards carbohydrate oxidation is observed with increasing exercise. Lactate is not only a waste product of skeletal muscle but also an important metabolic intermediate for mitochondrial oxidation. Lactate utilization refers to the metabolism of lactate to form pyruvate that can accumulate, be released from muscle, converted to alanine, be used to synthesize glycogen and be oxidized as fuel for energy metabolism. Using lactate as a tracer for carbohydrate metabolism is advantageous given the physiological concentrations that can be used and the fact that it leaves other oxidative process undisturbed.

Lactate metabolism in healthy rat skeletal muscle at rest was studied in different nutritional states using hyperpolarized  $[1-^{13}\text{C}]$ lactate. Lactate was polarized in a custom build 7T polarizer and injected in 8 healthy animals either fed or fasted overnight. Each animal was injected three times at 2h intervals.

Lactate metabolism was observed in terms of  $^{13}\text{C}$  label propagation into bicarbonate in fed animals and the absence of this metabolite in the fast state ( $p < 0.0001$ ), representing inhibition of the metabolic flux through pyruvate dehydrogenase. A significant difference in  $^{13}\text{C}$  labeling of pyruvate and alanine was observed comparing the fed and fasted group ( $p < 0.01$ ). No significant metabolic changes were observed following repeated lactate injections in the same animal. Bicarbonate detection was related to the initial signal-to-noise ratio of injected lactate and not to administered dose. Also, no dose dependencies were observed in the conversion to pyruvate and alanine.

This study shows for the first time that lactate is readily taken up by resting skeletal muscle *in vivo* and quickly converted to pyruvate for subsequent oxidation in the mitochondrion. The metabolic conversion of lactate was sensitive to a simple alteration of nutritional state. Since lactate can be administered at physiological concentrations and does not disturb other oxidative processes, hyperpolarized  $[1-^{13}\text{C}]$ lactate is ideal for studying carbohydrate oxidation in skeletal muscle *in vivo*.



A. Spectra acquired from rat skeletal muscle after injecting hyperpolarized  $[1-^{13}\text{C}]$ lactate show the formation of alanine, pyruvate and  $^{13}\text{C}$  bicarbonate. B. Summed spectrum from a fed and fasted animal. \*Impurity in the  $[1-^{13}\text{C}]$ lactate solution.

C. Signal ratios of pyruvate and bicarbonate relative to alanine in fed (n=4) and fasted (n=4) animals.