Physiological insulin-stimulated glucose utilization in skeletal muscle, glucose transport is the rate-limiting step. Furthermore, it has recently been shown that reduced insulin-stimulated glucose transport activity is the major step responsible for muscle insulin resistance in type 2 diabetes (7, 10).

As far as exercise-stimulated muscle glucose uptake is concerned, the actual magnitude in glucose uptake may be rather variable because it is influenced by a complex mixture of factors including type [e.g. dynamic (concentric, eccentric), static], intensity and duration of exercise, training status, energy status (e.g., high vs. low muscle glycogen level), availability of other substrates (e.g., FFA), species, and choice of experimental system (reviewed in Refs. 12, 15).

The diversity in maximum glucose uptake capacity between muscles with different fiber type composition is considered to be due to their different content of GLUT4 protein (4), suggesting that glucose transport is rate limiting. Furthermore, in perfused rat hindquarter muscle, subjected to maximum stimulating muscle contractions for 20 min, it took approximately 5 min from the onset of contractions to achieve maximum permeability of the plasma membrane for glucose (19). This was most likely the time needed to complete the GLUT4 translocation process. For the subsequent 15 min of continuous contractions, uptake of the phosphorylable glucose analog 2-deoxyglucose was constant over time in three different muscles with markedly different fiber type composition. This was in contrast to the nonmetabolizable analog 3-O-methylglucose, where apparent uptake rates rapidly decreased in a monoeponential fashion due to backflow out of the muscle cells of the nontrapped 3-O-methylglucose analog. This clearly shows that the hexokinase has the capacity to immediately phosphorylate all glucose that enters the cell through the maximum contraction-induced permeability increase of the muscle plasma membrane. This “sufficiency” capacity of the hexokinase is further supported by the lack of accumulation of any significant free intracellular glucose during exercise (8, 13), which would be expected if phosphorylation of glucose was rate limiting.

As noted above, glucose uptake in skeletal muscle is a saturable process. Transport of glucose through the muscle plasma membrane follows Michaelis-Menten kinetics. Estimated with 3-O-methylglucose zero-trans influx measurements, fiber type-dependent $K_m$ values of $5–17$ mM and $V_{\text{max}}$ values in excess of $14$-fold, compared with basal unstimulated muscle, have been found immediately after contractions in perfused rat muscle (11). These values reflect transport of glucose through GLUT4 proteins located in the muscle plasma membrane and compare very favorably with $K_m$ values of $5–13$ mM for GLUT4 expressed in heterologous systems like Xenopus oocytes and yeast cells (2, 17). After transport through the membrane, glucose is irreversibly phosphorylated by the hexokinase. Mammalian skeletal muscles contain two hexokinase isozymes. In rat skeletal muscle, the predominant type is hexokinase II, whereas in human skeletal muscle hexokinase I accounts for around three-fourths of total hexokinase activity (Ref. 14 and references therein). $K_m$ values of 0.03 mM for type I and 0.3 mM for type II hexokinases are found in vitro (18), which are at least $15$- to $150$-fold lower than $K_m$ for endogeneous muscle GLUT4. Let us suppose for the sake of argument that we remove the entire muscle plasma membrane. In that case, as soon as glucose leaves the capillaries, it will encounter the hexokinases without any intervening barriers and
kinetic measurements would be expected to yield a $K_m$ somewhere below 0.3 mM (the sum of contributions from parallel positioned type I and type II hexokinases). However, kinetic measurements for glucose uptake during in vivo exercise have rendered $K_m$ values of 5 mM in dog muscle (20) and 10 mM in human muscle (15). These $K_m$ values reflect the combined contribution from two serial connected systems, the plasma membrane and the intracellular hexokinases, and are similar to the $K_m$ value for the plasma membrane and very far from the $K_m$ for the hexokinases. Thus there is no contribution whatsoever from the hexokinases to the “combined” in vivo $K_m$, which, however, would be the case, if glucose phosphorylation is a significant barrier to glucose uptake by the working muscle.

Endurance training results in a significant adaptive increase in skeletal muscle hexokinase activity and GLUT4 protein content, which results in an increased glucose transport and glucose uptake capacity (1, 5). One can argue, keeping the topic of the present discussion in focus, that in case there was an “unneeded” excess amount of GLUT4 compared with hexokinase in untrained muscle, then it should be unnecessary for muscle to increase the expression of GLUT4 in response to endurance training to obtain an increased glucose uptake capacity. However, preventing the training-induced increase in muscle GLUT4 protein by administration of a long-acting $\beta_2$-adrenergic agonist before each training session results in inhibition of the normal training-induced increase in muscle glucose uptake (6), which demonstrates that glucose transport in skeletal muscle is rate limiting.

In summary, five arguments have been presented to support the notion that glucose transport is rate limiting for glucose uptake by the working muscle.

1) Expression of GLUT4 in different muscles correlates with maximum transport capacity.
2) Uptake rate of 2-deoxyglucose in exercising muscle is constant with time.
3) There is no significant accumulation of free intracellular glucose during contractions.
4) $K_m$ for glucose uptake in exercising muscle does not reflect any contribution from hexokinase.
5) Prevention of exercise training-induced increase in GLUT4 protein inhibits the normal training-induced increase in muscle glucose uptake.

Based on this, it is very unlikely that phosphorylation of glucose by hexokinase is a significant barrier to glucose uptake by the working muscle.

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REBUTTAL FROM DR. WASSERMAN AND FUEGER

Our rebuttal is keyed to the five summary arguments in the Counterpoint of Drs. Ploug and Vinten (6).

1) Expression of GLUT4 . . . maximum transport capacity. This is correct, but irrelevant to the argument at hand. GLUT4 is undoubtedly important for muscle glucose uptake (MGU). This does not preclude that glucose phosphorylation by hexokinase is a barrier. Figure 1 of our Point statement illustrates the relationship between GLUT4 and removal of 2-deoxyglucose (2-DG) by exercising mouse muscle and that this relationship is amplified by increased hexokinase.