Thiazolidinediones inhibit the transport activity of the mitochondrial pyruvate carrier proteins MPC-1 and MPC-2

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Abstracts

MPC-1 and MPC-2 were recently identified as essential components of the mitochondrial pyruvate transporter [1,2]. Here we report that thiazolidinediones (TZDs), which promote insulin sensitization in human skeletal muscle and increase the capacity to oxidize fatty acids, are acute inhibitors of pyruvate transport.

As PPAR-γ agonists, TZDs can also cause marked side effects that can be clinically prohibitive, such as plasma volume expansion, increased adiposity, congestive heart failure, and cardiovascular risk. Existing TZDs (rosiglitazone and troglitazone) and a prototype, PPAR-γ-selective compound (MDSC-0160) selectively inhibit pyruvate oxidation in permeabilized rodent myocytes (primary and immortalized cultures) and patient-derived, permeabilized skeletal muscle myocytes. Clinically relevant drug concentrations (1 μM<Ki<9 μM) selectively inhibit pyruvate-driven respiration, but have no effect on oxidation of other complex I-linked substrates or succinate. Moreover, the respiratory inhibition can be rescued upon addition of methyl pyruvate, indicating that pyruvate dehydrogenase activity is unaffected.

Permeabilized C2C12 myoblasts show significantly compromised pyruvate-driven respiration upon shRNA knockdown of either MPC-1 or MPC-2. No respiratory defect is observed on a variety of other substrates, and the respiratory rate can be significantly restored with methyl pyruvate.

Furthermore, acute knockdown of either MPC-1 or MPC-2 left-shifts the dose–response curve for both TZDs and the highly specific MPC inhibitor UK5099, indicating that the MPC complex is indeed a target of modulation by TZDs. Experiments to determine the mechanism by which pyruvate transport relates to insulin-sensitization are underway.

In summary, these results provide two principal observations: (1) a rigorous, biochemical validation of MPC-1 and MPC-2 as obligatory components of the mitochondrial pyruvate transporter, and (2) the first demonstration that TZDs acutely inhibit pyruvate transport at clinically relevant concentrations.

References

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