Acute mTOR inhibition induces insulin resistance and alters substrate utilization inăvivo

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The effect of acute inhibition of both mTORC1 and mTORC2 on metabolism is unknown. A single injection of the mTOR kinase inhibitor, AZD8055, induced a transient, yet marked increase in fat oxidation and insulin resistance in mice, whereas the mTORC1 inhibitor rapamycin had no effect. AZD8055, but not rapamycin reduced insulin-stimulated glucose uptake into incubated muscles, despite normal GLUT4 translocation in muscle cells. AZD8055 inhibited glycolysis in MEF cells. Abrogation of mTORC2 activity by SIN1 deletion impaired glycolysis and AZD8055 had no effect in SIN1 KO MEFs. Re-expression of wildtype SIN1 rescued glycolysis. Glucose intolerance following AZD8055 administration was absent in mice lacking the mTORC2 subunit Rictor in muscle, and inăvivo glucose uptake into Rictor-deficient muscle was reduced despite normal Akt activity. Taken together, acute mTOR inhibition is detrimental to glucose homeostasis in part by blocking muscle mTORC2, indicating its importance in muscle metabolism inăvivo.
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