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RITONAVIR ACUTELY INDUCES INSULIN RESISTANCE IN HEALTHY NORMAL VOLUNTEERS

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GA Lee¹, DD Mafong², JC Lo¹, JM Schwarz¹, FT Aweeka¹, K Mulligan¹, M Schambelan¹, and C Grunfeld¹

¹ University of California San Francisco, San Francisco, Calif., USA; and ² University Hospitals of Cleveland, Cleveland, OH, USA

BACKGROUND: Some HIV protease inhibitors acutely cause insulin resistance even in the absence of HIV infection, hyperlipidaemia or changes in body composition. Several protease inhibitors acutely inhibit the activity of the insulin-responsive glucose transporter GLUT4 *in vitro*. Previously, a single dose of indinavir was shown to decrease insulin-mediated glucose disposal in healthy normal volunteers. Here we report that a single dose of ritonavir also decreases insulin-mediated glucose disposal in humans.

METHODS: In this randomized, double-blind, cross-over study, a single dose of ritonavir 800 mg or placebo was given to six healthy HIV-negative men 2 h before assessment of insulin sensitivity by euglycaemic hyperinsulinaemic clamp. Subjects reached therapeutic ritonavir levels at the start of the clamp. Free fatty acid levels and substrate oxidation rates were measured during the clamp study.

RESULTS: There were no significant differences in body weight, fasting plasma glucose, serum insulin or lipid levels before each study. During steady-state (120 to 180 min), serum insulin reached levels of 606 ± 40 and 577 ± 52 pmol/l during placebo and ritonavir administration, respectively. Glucose was maintained at approximately 4.4 mmol/l under both conditions. The average concentration of ritonavir reached therapeutic levels during steady state (10.9 ± 0.7 μ M), and the 3-h area under the curve (AUC) was 33.4 ± 4.4 μ M/h. Insulin-mediated glucose disposal per unit insulin decreased by 21% (from 10.1 ± 0.9 to 8.0 ± 0.8 mg/kg-min per μ U/ml insulin, $P=0.02$). The non-oxidative component of total glucose disposal decreased by 30% (from 6.1 ± 0.5 to 4.3 ± 0.5 mg/kg-min, $P=0.0004$). Ritonavir 3-h AUC correlated with the percent change in non-oxidative glucose disposal

($r = -0.90$, $P = 0.01$). Free fatty acid levels were not significantly different at baseline and were suppressed similarly with insulin administration during both studies.

CONCLUSIONS: A single dose of ritonavir in HIV-negative men decreased total and non-oxidative insulin-mediated glucose disposal as assessed by the euglycaemic hyperinsulinaemic clamp. The percentage decrease in non-oxidative glucose disposal was correlated with ritonavir drug levels. These data suggest that insulin resistance will worsen further with supra-therapeutic drug levels; excess levels might be avoided with therapeutic drug monitoring.

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