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INDINAVIR INCREASES HEPATIC GLUCOSE PRODUCTION IN HEALTHY HIV-NEGATIVE MEN

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OBJECTIVES: HIV protease inhibitor therapy is associated with abnormalities in glucose metabolism including peripheral insulin resistance. In studies performed in HIV-negative volunteers to differentiate the direct effects of indinavir from those related to HIV infection itself, we found that 4 weeks of indinavir treatment caused glucose intolerance and decreased insulin-mediated glucose disposal and storage. These changes are consistent with an effect of indinavir on GLUT4. This study reports the effects of indinavir on hepatic glucose metabolism, which was quantified in nine of these subjects.

METHODS: Hepatic glucose production (HGP), glycogenolysis and gluconeogenesis were measured using stable isotope tracer techniques in nine healthy HIV-negative men before and at the end of treatment with indinavir, 800 mg three times daily. Measurements were made under conditions of both fasting and hyperinsulinaemia (euglycaemic hyperinsulinaemic clamp).

RESULTS: Fasting HGP increased with indinavir (12.6 ± 0.3 vs 13.5 ± 0.3 mmol/kg*min; $P < 0.03$). This increase was driven by proportional contributions of glycogenolysis (9.5 ± 0.3 vs 10.2 ± 0.3 $\mu\text{mol/kg*min}$, $P < 0.03$) and gluconeogenesis (3.0 ± 0.2 vs 3 ± 0.2 $\mu\text{mol/kg*min}$, $P < 0.14$). Both glycogenolysis and gluconeogenesis measured during the clamp were higher after 4 weeks of indinavir (4.7 ± 0.9 vs 6.6 ± 1.2 $\mu\text{mol/kg*min}$, $P < 0.02$; 0.2 ± 0.03 vs 0.3 ± 0.04 $\mu\text{mol/kg*min}$, $P < 0.009$, respectively). The increase in glycogenolysis accounted for 75% of the increase in fasting HGP and 96% of the impairment in insulin suppression of HGP seen with indinavir.

CONCLUSIONS: Four weeks of treatment with indinavir increases fasting HGP moderately and blunts the suppression of HGP by insulin. Glycogenolysis plays a major role in the increase in HGP in both fasting and hyperinsulinaemia. These results cannot be explained by an effect of indinavir on GLUT4 alone; therefore, other mechanisms must be involved. Hepatic insulin resistance contributes to the effects of indinavir on altered glucose metabolism.

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7

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