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DIFFERENTIATION OF ATAZANAVIR FROM OTHER HIV-PROTEASE INHIBITORS IN PRECLINICAL MODELS OF GLUCOSE UPTAKE, LIPOGENESIS AND PROTEASOME FUNCTION

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BACKGROUND: Atazanavir is an HIV-protease inhibitor (PI) in development which shows antiviral efficacy without plasma lipid disturbances seen with other PIs.

OBJECTIVES: To elucidate the mechanisms for the apparent metabolic differences between atazanavir and other PIs in relation to current hypotheses for metabolic disturbances in HIV-PI therapy.

METHODS: Cell models: 3T3-L1 adipocytes, mouse primary adipocytes, L6 myocytes (myotubes), and human HepG2 hepatocytes. PIs (purified) were: ritonavir, lopinavir, saquinavir, nelfinavir and indinavir. Assays: 2-3H-deoxyglucose uptake, 1-¹⁴C-acetate incorporation into cellular triacylglycerol (TG), TG accumulation by enzymatic methods and human 20S proteasome chymotryptic activity assayed by fluorogenic peptide.

RESULTS: PIs exhibited effects in these models at physiologically relevant concentrations (~2-40 μM). Insulin-stimulated glucose transport (GLUT4) in both adipocytes and myocytes was markedly inhibited by several PIs, with rank order of inhibition potency lopinavir~ritonavir>saquinavir>nelfinavir>indinavir> atazanavir. Atazanavir had essentially no effect on glucose transport. The rank order for TG synthesis inhibition potency in adipocytes was nelfinavir>lopinavir>saquinavir>ritonavir>indinavir~ atazanavir. In HepG2 cells, nelfinavir and ritonavir promoted TG synthesis >twofold while atazanavir had no effect. Proteasome assays revealed marked inhibition for several PIs, with rank order saquinavir>nelfinavir> lopinavir>ritonavir>atazanavir>indinavir.

CONCLUSIONS AND DISCUSSION: PIs were readily differentiated in assays of glucose transport, lipogenesis and proteasome activity. The data indicate differential interference with two key molecular mechanisms (previously proposed by others), GLUT4 inhibition and proteasome inhibition. GLUT4 is necessary for insulin sensitivity. Proteasome is relevant to lipogenesis through its role in apolipoprotein B degradation in liver (critical to VLDL secretion and plasma TG levels) and in degradation of the key lipogenic transcription factor SREBP-1. The data support these mechanisms linking certain PIs with insulin resistance, dyslipidemia, and fat redistribution. Atazanavir exhibited the least interference among PIs tested in these models, providing a potential explanation for its advantageous plasma lipid profile in the clinic.

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10

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