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MECHANISMS OF INSULIN RESISTANCE IN HIV-SERONEGATIVE INDIVIDUALS ACUTELY TREATED WITH RITONAVIR BOOSTED INDINAVIR AND ATAZANAVIR REGIMENS

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DA Doran¹, SP Jones^{1,2}, C Lagathu³, L Evans⁴, IT Cambell⁴, DJ Stokes¹, AP Yates⁵, M Caron³, M Pirmohamed², DJ Back², SH Khoo² and DP Maclaren¹

¹ Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK; ² Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK; ³ INSERM Unit, CHU St Antoine, Paris, France; ⁴ University Hospital of South Manchester, Department of Anaesthesia, Manchester, UK; and ⁵ Clinical Research Department, Manchester Royal Infirmary, Manchester, UK

BACKGROUND: Protease inhibitor (PI) therapy has been associated with differential effects on lipid and glucose metabolism. Single dose indinavir (IDV) induces insulin resistance in HIV-seronegative men presumably by blockade of the insulin responsive glucose transporter GLUT4. By contrast, atazanavir has not been associated with altered lipid or glucose metabolism nor with inhibition of GLUT4 *in vitro*. In this three-arm study, we compared the effects of a single dose of boosted atazanavir/ritonavir (ATV/RTV), indinavir/ritonavir (IDV/RTV) and placebo on insulin and exercise stimulated glucose disposal, GLUT4 mRNA and protein expression.

METHODS: Eighteen healthy male volunteers (25.6 ± 5.1 years) were randomly allocated to a single dose of placebo (*n*=6), ATV/RTV (300/100 mg) (*n*=6), or IDV/RTV (800/100 mg) (*n*=6). One hour after drug administration, subjects performed 60 mins of cycling at 70% of VO_{2max}. They then underwent a 180 mins euglycaemic hyperinsulinaemic clamp to assess the effects on insulin sensitivity, glucose disposal and free fatty acids (FFA). At baseline, 60 mins and post-exercise a percutaneous needle muscle biopsy was performed.

RESULTS: There were no significant differences in plasma glucose, insulin and FFA between the placebo, IDV/RTV or ATV/RTV arms at baseline or during the clamp. ATV and IDV plasma concentrations were within the expected range at 60 mins and remained so until the end of the clamp. Insulin-stimulated glucose disposal per unit of insulin (M/I) was significantly reduced in the IDV/RTV group (8.19 ± 0.3) when compared with both

the placebo ($12.1 \pm 1.0 \text{ mg}\cdot\text{kg}\cdot\text{min}^{-1}$ per $\mu\text{U}/\text{ml}$, $P < 0.05$) and ATV/RTV ($14.58 \pm 1.0 \text{ mg}\cdot\text{kg}\cdot\text{min}^{-1}$ per $\mu\text{U}/\text{ml}$, $P < 0.05$) arms. The non-oxidative component of total glucose disposal (storage) was lower in the IDV/RTV group ($3.74 \pm 0.42 \text{ mg}\cdot\text{kg}\cdot\text{min}^{-1}$), when compared with the placebo ($5.62 \pm 0.60 \text{ mg}\cdot\text{kg}\cdot\text{min}^{-1}$) and ATV/RTV arms (5.40 ± 0.53) $P < 0.01$. Total GLUT4 mRNA and protein did not decrease in either IDV/RTV or ATV/RTV groups when compared with placebo.

CONCLUSIONS: IDV/RTV, but not ATV/RTV, acutely induces insulin resistance, an effect which is not mediated by direct inhibition of GLUT4. The effect of these drugs *in vivo* on the intrinsic activity of GLUT4 warrants further investigation.

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