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IRBESARTAN, AN ANGIOTENSIN II RECEPTOR I BLOCKER, PREVENTS THE ADVERSE EFFECTS OF HIV ANTIRETROVIRALS ON ADIPOCYTE FUNCTIONS

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OBJECTIVES: Some HIV-antiretrovirals can induce adipocyte dysfunction leading to insulin resistance, lipid disorders and lipodystrophy in HIV-infected patients resulting in an increased risk of cardiovascular disease. Irbesartan (IRB), an antihypertensive angiotensin II type 1 receptor (ATR-1) blocker, recently shown to activate PPAR γ in adipocytes and to reduce the incidence of diabetes mellitus in hypertensive patients. Whether IRB can reverse the effects of some HIV antiretrovirals on murine culture adipocytes is unknown.

METHODS: We evaluated the effects of irbesartan (IRB, 10 μ M) on 3T3-F442A murine adipocytes pretreated with a series of protease inhibitors used alone (indinavir, IDV, amprenavir, APV) or in association with a low dose of ritonavir (RTVr) (lopinavir, LPVr, atazanavir, ATVr) used at near- C_{max} concentrations. We checked in differentiating adipocytes, lipid accumulation and insulin signalling.

RESULTS: We confirmed that IDV, LPVr and ATVr decreased the lipid content of differentiating 3T3-F442A adipocytes whereas APV and the (ATR-1) blocker, IRB used alone had no effect. Co-treatment of PI-treated cells with IRB suppressed the effect of IDV and partially decreased the effect of ATVr on lipogenesis and lipid accumulation while it did not alter the effect of LPVr. IDV, LPVr and ATVr induced insulin resistance by decreasing insulin induced tyrosine phosphorylation of the insulin receptor (IR)- β -subunit, its major substrate IRS-1 and of the MAP kinases, ERK 1/2. The protein expression of two major transcription factors involved in adipogenesis and insulin response, C/EBP α and PPAR γ was also altered. The addition of IRB reversed all this alterations. The inhibitory effect of IDV, LPVr and ATVr on insulin activation of glucose

transport was almost totally prevented by IRB. AT1 receptor protein level was increased by IDV, LPVr and ATVr, which was completely prevented by IRB.

CONCLUSIONS: Irbesartan can reverse the effects of protease inhibitors on lipid accumulation, differentiation and insulin signalling in murine adipose cell lines. The beneficial effect of IRB, particularly on insulin response, will be evaluated *in vitro* in human adipocytes treated with protease inhibitors. These results could benefit to HIV-infected patients with antiretroviral related lipodystrophy and insulin resistance.

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