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ALTERED ADIPOCYTOKINE GENE EX-PRESSION IN MURINE 3T3-F442A ADIPOCYTES TREATED WITH PROTEASE INHIBITORS AND NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

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BACKGROUND: Protease inhibitors (PIs) can impede the differentiation of pre-adipocytes. The mechanisms of this are not well understood, although modulation of cytokine secretion may be involved. In order to further investigate this, we have investigated the effects of PIs and zidovudine and stavudine on gene expression of the adipocytokines TNF-α, IL-6 and adiponectin.

METHODS: We incubated differentiating murine 3T3- F442A adipocytes in the presence (20 µM) or absence of zidovudine, stavudine and the PIs indinavir, ritonavir and saquinavir. The effect of these drugs either in isolation or in combination with rosiglitazone (10 µM) on TNF-α, IL-6 and adiponectin mRNA expression were assessed using quantitative real-time PCR. Differences in expression were assessed using the ΔCT method and normalized to β-actin.

RESULTS: The mRNA expression of adiponectin was significantly reduced in both nucleoside reverse transcriptase inhibitor (NRTI)- and PI-treated cells, although the most profound reductions were found with ritonavir and saquinavir (–7.5- and –8.2-fold vs control, respectively, $P<0.001$). In contrast, IL-6 mRNA levels were markedly enhanced by ritonavir and saquinavir (17.85- and 28.54-fold vs control, respectively, $P<0.001$), whilst the NRTIs and indinavir had minimal effects. Similarly, TNF-α gene expression was also significantly increased in PI-treated cells, although zidovudine, stavudine and indinavir (9.8-, 8.46-, 10.84-fold change vs control, respectively) were also found to up regulate expression. Co-incubation with rosiglitazone led to a partial attenuation in TNF-

α mRNA levels with all of the treatments; however, this was not in relation to IL-6 and adiponectin gene expression.

CONCLUSIONS: Our data suggest that the PIs ritonavir and saquinavir have potent effects in up-regulating TNF-α and IL-6 mRNA levels, whilst decreasing adiponectin levels. The co-administration of the PPAR agonist rosiglitazone was found to partially attenuate the increased expression of TNF-α, but not IL-6 or adiponectin. Our results suggest that the metabolic abnormalities associated with PI use are, at least partially, related to effects on adipocytokine gene expression.

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