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PREVENTION OF PROTEASE INHIBITOR-INDUCED ADIPOCYTE CYTOTOXICITY BY POLYUNSATURATED FATTY ACIDS AS A MODEL OF TREATMENT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY-INDUCED LIPODYSTROPHY

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JC Domingo¹, B Cordobilla¹, F Villarroya¹, M Giral¹, MA de Madariaga¹ and P Domingo²

¹Department of Biochemistry and Molecular Biology, University of Barcelona, Barcelona, Spain; and ²Institut de Recerca de la Santa Creu i Sant Pau, Barcelona, Spain

BACKGROUND: Individuals receiving antiretroviral therapy for the treatment of HIV-1 infection experience peripheral lipoatrophy, gain in visceral fat, hyperlipidaemia and insulin resistance, all of which have been grouped under the common heading of HIV-associated lipodystrophy. The pathogenesis of lipodystrophy is likely to involve numerous mechanisms, such as the inhibition of DNA polymerase gamma in mitochondria by nucleoside reverse transcriptase inhibitors, abnormalities of fat differentiation resulting from the effects of protease inhibitors (PIs) on transcription factors such as sterol regulatory element-binding protein-1 (SREBP1) and increased apoptosis of fat cells secondary to these many insults. Polyunsaturated fatty acids (PUFAs) have been shown to be effective in reducing metabolic abnormalities associated with increased SREBP1 activities. We have studied the effect of the PUFAs on the viability and apoptosis of adipocytes in cell culture induced by nelfinavir as a model of PI-induced lipodystrophy *in vitro*.

METHODS: MTT method was used to assess the cellular viability of 3T3-L1 adipocytes in the presence of nelfinavir with or without different PUFAs [18:1(n-9), 18:2(n-6) and 22:6(n-3)] incorporated on structurally different compounds (free fatty acid, triglyceride, diglyceride and ethyl ester). Cell apoptosis was measured by annexin-V and propidium iodide staining and samples were analysed using a FACSCalibur flow cytometer (Becton Dickinson, San Jose, CA, USA).

RESULTS: Exposure of 3T3-L1 adipocytes to a clinically relevant concentration of nelfinavir (20 μ M) decrease the cell viability (-88% vs control) and promote cell apoptosis (70% of apoptotic cells vs 10% in control cells). Furthermore, the triglycerides rich in n-3 and n-6 PUFAs prevent the nelfinavir-induced alteration of cellular viability/apoptosis in a dose-dependent manner with an order of inhibition potency of 22:6(n-3)>18:2(n-6). The nelfinavir-induced cytotoxic effect was not inhibited by 18:1(n-9) triglyceride. However, the inhibition profile seen with the 22:6(n-3) free fatty acid was minimal (and often non-existent) when compared to the effect of 22:6(n-3) ethyl ester or diglyceride. Interestingly, the nelfinavir-induced cytotoxicity was markedly reduced by the 18:2(n-6) free fatty acid, whereas the consumption of 18:1(n-9) had no effect.

CONCLUSIONS: These results (protected under a patent application by PE Brudy, SL) suggest the concept that n-3 and n-6 PUFAs treatment could inhibit adipocyte PI-induced cytotoxicity by suppressing the expression of SREBP-1 as well as having a well established role as ligands for peroxisome proliferators activated receptors. This might open up a new aspect of nutritional therapy application involving PUFAs as inhibitors of PI-induced lipid abnormalities.

Presenting author: P Domingo

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