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Efavirenz induces alterations in lipid metabolism through AMPK activation

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Background

Recent evidence suggests that the NNRTI efavirenz (EFV) contributes to changes in lipid and body fat composition that are implicated in lipoatrophy. As the liver is an important organ in lipid metabolism, we have evaluated the effects of clinically-used concentrations of EFV on mitochondrial function and cellular lipid metabolism in vitro, and the implication of AMP-activated protein kinase (AMPk), the master switch for regulation of cellular bioenergetics, in these processes.

Methods

O2 consumption in non-HIV infected Hep3B cells was measured with a Clark-type electrode. Following incubation (1 hr) with EFV (10, 25 or 50 μM), intracellular ATP was measured by fluorescence, mitochondrial membrane potential (Δψm), indicative of mitochondrial function, was analyzed by static cytometry, and AMPK was evaluated by Western blotting. In order to further study the implication of this enzyme, selected experiments were performed in cells pretreated (30 min) with the AMPK inhibitor Compound C (20 μM). The expression of the fatty acid transporter CD36 was analyzed by PCR, and the intracellular lipid content was determined by nuclear magnetic resonance (NMR) after 4 hr incubation with EFV.

Summary of results

EFV produced an immediate reduction of mitochondrial function, evident by the significant and dose-dependent inhibition of mitochondrial O2 consumption and the decrease of intracellular ATP and Δψm. This metabolic stress promoted the activation of AMPK, triggering several of its signalling pathways, as EFV induced an increment in CD36 mRNA expression and in intracellular lipid content, which could have been a result of the formation of lipid droplets. This intracellular lipid increase was not present in cells treated with Compound C, which points to a key role for AMPK in these mechanisms.

Conclusion

Given that EFV treatment is usually prolonged, these mechanisms may effect the general regulation of lipid metabolism and could cause the alterations that are characteristic of lipoatrophy.

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