ABSTRACT:

Título del resumen:

A differential bioenergetic effect in human glia and neurons under treatment with the antiretroviral drug Efavirenz

Texto del resumen:

The differential response of neurons and astrocytes to energy depletion is key to understanding the extreme vulnerability of neurons to rapid fluctuations in bioenergetics and the presence of mitochondrial damage. Efavirenz (EFV) is one of the most widely prescribed anti-HIV-1 drugs. Although generally considered safe, up to 50% of patients on EFV exhibit a wide range of CNS-related symptoms, the mechanisms of which remain unknown. Here we analyse the differential bioenergetic effect of EFV in human neurons and glia cells. Short-term treatment (up to 24h) of glial and neuronal cultures with clinically relevant concentrations of EFV compromised cell viability, particularly so in neurons, and disrupted mitochondrial function by undermining O2 consumption, reducing mitochondrial membrane potential and increasing reactive oxygen species generation. In order to simulate a milieu of compromised mitochondria and/or a proinflammatory state in the brain, we assessed the effect of EFV in the presence of exogenous NO (by adding the NO-donor DETA-NO). We observed that the inhibitory effect of EFV was enhanced. Moreover, the mitochondrial interference triggered by EFV led to a major bioenergetic switch in glia cells triggering AMPK activation and glycolysis up-regulation (increased ATP generation and lactate production) and these actions were not observed in neurons. Of note, the glycolytic effect of EFV in glia cells was strengthened in the presence of DETA-NO. Based on these results, we conclude, that EFV modifies the energy metabolism of neurons and glia and that this cell type-specific response could be implicated in the mechanisms underlying of the neurological adverse events observed in EFV-treated patients.

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