Abstract Oral Communication
SYMPOSIUM NEUROPSICHIATRY & HIV

Barcelona, June 13th and 14th, 2014

Efavirenz increases nitric oxide production in glia cells but not in neurons

Presentation not available

BACKGROUND: 50-90% of patients treated with Efavirenz (EFV) exhibit CNS-related effects which often lead to discontinuation of the therapy, and the underlying mechanisms are unknown. Of note, there is a substrate of CNS inflammation during HIV infection related to HIV-related cognitive disorders. During inflammation, high amounts of nitric oxide (NO) are produced following the up-regulation of the inducible isoform of nitric oxide synthase (iNOS) in inflammatory activated cells. NO exerts cytotoxic effects and one of its actions includes interference with the mitochondrial respiratory chain. We analysed if EFV has the ability to regulate NO expression in neurons and glia.

METHODS: Human cell lines (glioma and neuroblastoma) and rat primary cultures of astrocytes and neurons were treated with clinically relevant concentrations of EFV for a short period of time (6-24h). NOS expression was studied by immunoblot, NO production was assessed by fluorescence microscopy and mitochondrial O2 consumption was evaluated using Clark type O2 electrode.

RESULTS: Analysis of NOS revealed that EFV treatment led to an increased expression of iNOS in U-251MG cells and the enhanced generation of NO was confirmed by the fluorescent marker DAR-4M. On the contrary, neurons did not exhibit increase in neither nNOS expression nor NO production. The up-regulation of the intracellular NO content was corroborated in primary rat astrocytes. Next, we observed that EFV-induced NO interferes with mitochondrial O2 consumption, as the respiration deficiency provoked by this drug in glia cells was partially recovered when EFV was co-administered with L-NAME, a pharmacological inhibitor of NOS.

CONCLUSION: Our results indicate that in glia cells, but not in neurons, EFV induces an increase in the intracellular level of NO which compromises the mitochondrial O2 consumption. These findings may contribute to the understanding of the molecular mechanisms of EFV-induced neurotoxicity, a phenomenon of great clinical relevance.

AUTHOR 1:
Haryes A Funes. Departamento de Farmacología, Facultad de Medicina, Universidad de Valencia, Valencia, Spain

AUTHOR 2:
Fernando Alegre. FISABIO-Hospital Universitario Dr. Peset, Valencia, Spain; Facultad de Medicina, Universidad de Valencia, Valencia, Spain

AUTHOR 3:
Miriam Polo. FISABIO-Hospital Universitario Dr. Peset, Valencia, Spain; Facultad de Medicina, Universidad de Valencia, Valencia, Spain

AUTHOR 4:
Ana Blas-García. FISABIO-Hospital Universitario Dr. Peset, Valencia, Spain; Facultad de Medicina, Universidad de Valencia, Valencia, Spain

AUTHOR 5:
Juan V. Esplugues. FISABIO-Hospital Universitario Dr. Peset, Valencia, Spain; Facultad de Medicina, Universidad de Valencia, Valencia, Spain; CIBERehd

AUTHOR 6:
Nadezda Apostolova. Facultad de Ciencias de la Salud, Universitat Jaume I, Castellon, Spain; CIBERehd