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P273

Anti retroviral drugs rilpivirine and efavirenz cause cardiovascular dysfunction: role of endoplasmic reticulum stress

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The HIV infected population is at an increased risk of cardiovascular morbidity and mortality in comparison to the uninfected population, the cause of which is not fully understood but is likely to be due to interplay between the human immunodeficiency virus, antiretroviral therapy and traditional risk factors.

In the present study we investigated and compared the cardiovascular effects of the non nucleoside reverse transcriptase inhibitors (NNRTI) efavirenz (EFV), a component of the widely used once a day Atripla therapy, to the 2nd generation NNRTI rilpivirine (RPV), a component of the new once a day Complera therapy.

The rat heart H9C2 cell line was exposed to different concentrations of RPV and EFV (3, 10, 30μM) for 24 or 48h. Cell viability was measured using the MTT assay while apoptosis and necrosis were assessed by morphological analysis following propidium iodide/ hoescht staining. Data was expressed as mean±SEM from n = 3 or 4 experiments (2-6 replicates per experiment), statistical analysis was carried out by one or two way ANOVA where $p<0.05$ was considered significant.

A concentration dependent loss of cell viability was measured following 24h and 48h exposure to both NNRTIs. Both EFV and RPV reduced cell viability in a dose and time dependent manner. Cell viability was reduced to 48±4.3% and 60±1.4% following 24h exposure to 30μM EFV and RPV respectively ($p<0.05$ vs. untreated cells). Both EFV and RPV dose-dependently increased cell necrosis, however, only EFV increased cell apoptosis. EFV and RPV 30 μM increased necrosis from 0.57% to 10.95±1.8% and 26.7±9.1% respectively ($p<0.05$). Apoptosis was increased from 0.041±0.026% to 4.0±1.5%, with 30μM EFV ($p <0.05$).

Recently endoplasmic reticulum (ER) stress has been implicated in number of various cardiovascular diseases such as cardiac hypertrophy, heart failure, atherosclerosis and ischaemic heart disease. Protease inhibitors, another group of anti HIV medication has been shown to cause ER stress in hepatocytes and adipocytes. To determine whether the loss of cell viability and increased cell death following NNRTI exposure was mediated by ER stress we measured the expression of the ER stress marker protein, CHOP, in H9c2 cells by Western blotting following 24h exposure to EFV and RPV. Treatment with either drug increased protein levels of CHOP in comparison to untreated cells.

In conclusion both NNRTIS EFV and the newer RPV cause heart cell damage, which may be mediated by increased ER stress. This is the first time NNRTIs have been shown to cause ER stress in any cell type, and may suggest a possible mechanism for NNRTI mediated cell dysfunction.