The effect of valproic acid (VPA) on activated T lymphocytes[1]

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Background

VPA is an established and widely used drug for the treatment of epilepsy. Many cellular pathways are affected from VPA and recently, it was discovered that it acts as an inhibitor of histone deacetylases, regulating in this way gene expression through epigenetic mechanisms. At the same time, cells of the immune system constantly undergo a series of epigenetic alterations to respond to immune stimuli. Since VPA has been suggested to have an immunomodulatory role, and it is a drug continuously used in a variety of neurological disorders, this project was scheduled in order to investigate the functional effect of VPA on lymphocytes derived from normal individuals.

Methods

Freshly thawed peripheral blood mononuclear cells (PBMC) from 12 healthy individuals (7 males, 5 females) (mean±SD=25.3±8.7 yrs, range 17-44 yrs) were stimulated with phytohemaglutinin (PHA-L) in the presence of sub-toxic concentrations of VPA for 4 days (Figure 1). Viable cells were assessed for alterations in their cell surface phenotype as well as their cell cycle.

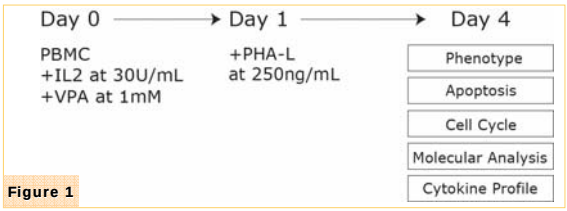


Figure 1

Results

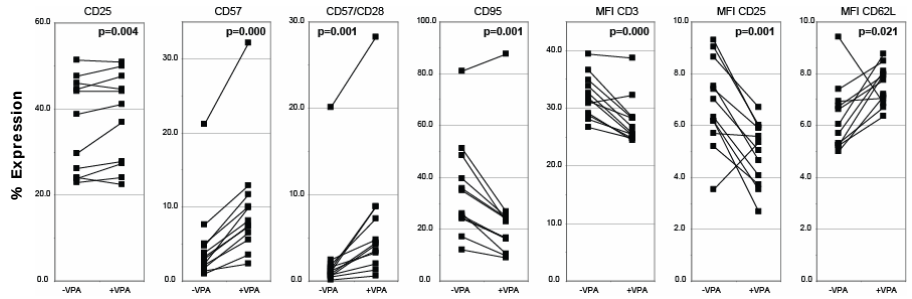


Figure 2 Alterations in the phenotype of CD4 T cells after culture with VPA. Cell surface expression of several molecules as well as changes in their mean fluoresence intensity (MFI) were examined. Statistically significant changes (Wilcoxon) are indicated.

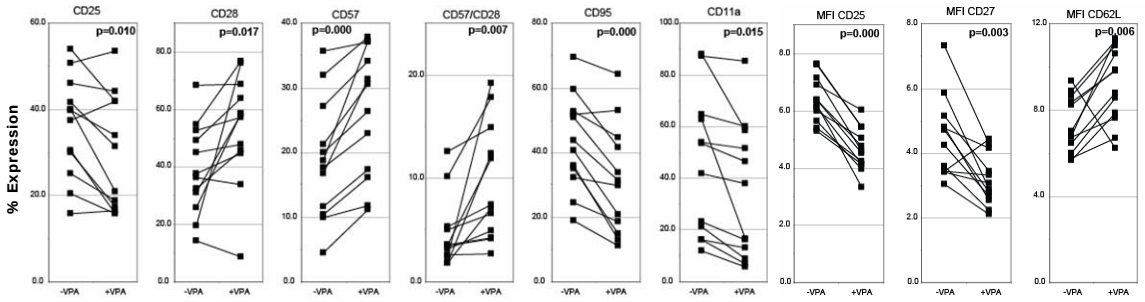


Figure 3 Culture with VPA, alters the phenotype of CD8 T cells. Cell surface expression of several molecules as well as changes in their mean fluoresence intensity (MFI) were examined. Statistically significant changes (Wilcoxon) are indicated.

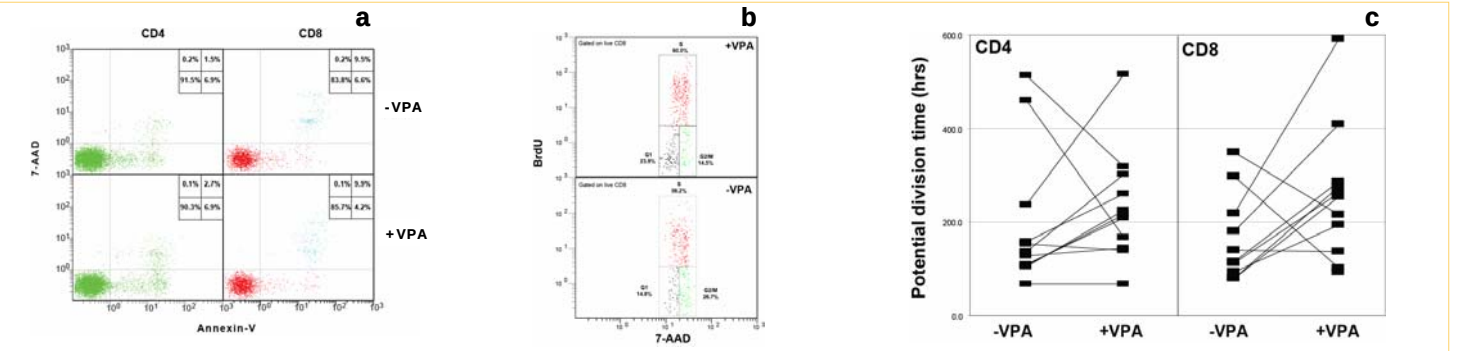
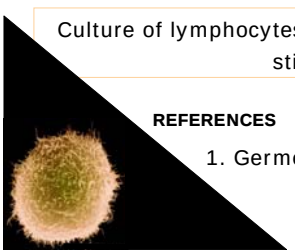


Figure 4 Culture with VPA affects the cell cycle of lymphocytes. The presence of VPA, although not toxic on CD4 and CD8 lymphocytes, as evident by AnnexinV/7-AAD staining (panel a), can interfere with cell cycle transition of both CD4 and CD8 T cells from the S to G2/M phase (panel b). Interestingly, the division time (estimated potential division time) of both CD4 and CD8 T cells was increased after culture with VPA (panel c), suggesting a direct effect on lymphocyte function.

Conclusion

Culture of lymphocytes in the presence of VPA has an immunomodulatory effect, coupled by an inability of cells to proliferate upon stimulation. This finding can impact on the immune response of patients treated with VPA.



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1. Germenis AE, Karanikas V. Immunol Cell Biol 2007, 85:55-59

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