PALMITOYLETHANOLAMIDE IMPROVES HIV-1 TAT-INDUCED DIARRHEA ACTING THROUGH SELECTIVE PPARalpha-DEPENDENT INHIBITION OF ENTERIC GLIAL CELLS ACTIVATION

1) Sarnelli G. 2) Gigli S. 3) Seguella L. 4) Steardo L. 5)Esposito G.

Sapienza University- Dept. Physiology and Pharmacology

Diarrhea represents the most common and serious feature of HIV-1 infected patients, due to enterotoxic effects mediated by HIV-1 trans activating factor protein (Tat) mainly (Canani et al., 2003). Enteric glial cells (EGCs) are involved in intestine immune-inflammatory responses, acting as antigen-presenting cells and releasing proinflammatory cytokines and factors, such as S100B and iNOS (Capoccia et al., 2015). Palmitoylethanolamide is an endogenous ALIAmide able to modulate EGCs activation through a PPAR□-dependent mechanism (Esposito et al., 2014). Aim of this study is to clarify the specific role of EGCs in onset of secretory diarrhea HIV-1 Tat-induced and, consequently, to evaluate the potential therapeutic effect of PEA administration.

Wistar rats and PPAR□-/- mice were used for the experiments. Animals were randomly divided in different experimental groups receiving vehicle, HIV-1 Tat, HIV-Tat plus daily PEA, HIV-Tat plus lidocaine, bisacodyl in some experiments. Additionally, rats received PEA in presence of selective PPAR□ and PPARγ antagonists. At day 7 after diarrhea induction, animals were euthanized and colons were isolated to assess histochemical and biochemical analysis. Parametric one-way analysis of variance (ANOVA) and Bonferroni's posthoc test were used to assess statistical analysis.

Intracolonic administration of HIV-1 Tat induced a significant increase in diarrhea symptoms together with a marked EGCs activation, as deduced by over-expression of specific glial markers (such as S100B and GFAP) and relative proinflammatory factors (for instance TLR-4, iNOS and nitrite release). PEA significantly reduced all the effects HIV-1 Tat-mediated in a PPAR□-dependent manner. Indeed, PPARγ antagonists didn't change PEA activity but in presence of PPAR□ antagonist and in PPAR□-/- mice PEA didn't display any significant effect. Lidocaine administration prevented the acute diarrhea induced by HIV-1 Tat EGCs activation. Conversely, bisacodyl, as non-immunological stimulus, didn't affect glial network and markers, and wasn't completely unaffected by PEA treatment.

EGCs display a critical role in the onset of diarrhea HIV-1 Tat-induced and, at the same time, sustain a severe immune-inflammatory state. These inflammatory responses are significantly counteracted by PEA, inhibiting upstream EGCs activation through a selective PPAR□-dependent mechanism. On the basis of these results, together with its clinical availability and manageability, PEA represents an intriguing candidate to treat diarrhea as addition in the current therapy against HIV infection.

Canani et al. (2003) Gastroenterology. 124, 368-376.

Capoccia et al. (2015) Int J Immunopathol Pharmacol. 28(4), 443-451.

Esposito et al. (2014) Gut. 63(8), 1300-1312.