

Illuminating biology at the nanoscale with super-resolution fluorescence microscopy

METGen-02-

Nuclear Peroxisome Proliferator Activated Receptor-alpha (PPAR α) has been proposed as a potential target for the treatment of neuroinflammation-associated neuropsychiatric disorders, including alcohol abuse, but direct experimental evidence is still weak. Ethanol binge induces neuroinflammation in frontal cortex that is prevented by several acylethanolamides, such as oleoylethanolamide and palmitoylethanolamide, by regulation of Toll Like Receptors 4 (TLR4)-associated inflammatory pathway in frontal cortex. These acylethanolamides acts mainly as endogenous PPAR α agonists, although they may bind other receptors, and direct evidence on the role of PPAR α in neuroinflammation is unknown. We aim to study the role of PPAR α in frontal cortex under physiological or neuroinflammation-associated ethanol binge challenge. Results indicated that PPAR α KO mice showed an increase in TLR4, Nuclear Factor- κ B p65 subunit, cyclooxygenase-2 (COX-2), interleukin-1 β (IL-1 β) and Tumor Necrosis Factor- α (TNF- α) mRNA levels in frontal cortex. After Drinking in the Dark ethanol administration we observed an increase in main inflammatory markers in the WT ethanol group as expected. However, ethanol animals lacking PPAR α receptors showed reduced levels of TLR4, p65, Cox-2 and IL-1 β mRNA levels compared with ethanol WT group. Additionally, PPAR α KO animals showed a compensatory upregulation of the PPAR γ isoform, which is also anti-inflammatory, primarily under ethanol stimulating conditions. Indeed, PPAR γ / α ratio in KO animals was bigger under ethanol challenge. Additionally, the PPAR γ endogenous ligand 15d-Prostaglandin J2 was similarly upregulated in KO animals, especially in ethanol-treated animals. Results highlight an anti-inflammatory homeostatic role of PPAR α in physiological conditions and indicate that the lack of PPAR α may induce a compensatory PPAR γ isoform up-regulation mainly. Results highlight an anti-inflammatory homeostatic role of PPAR α in physiological

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