

## CENTRAL PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR ALPHA MODULATES CARRAGEENAN-INDUCED PAW EDEMA IN MICE

D'Agostino G., La Rana G., Russo R., Sasso O., Iacono A., Esposito E., Cuzzocrea S. \*, Meli R. & Calignano A.

Department of Experimental Pharmacology, University of Naples "Federico II", Italy.

\* Department of Clinical and Experimental Medicine and Pharmacology, Messina, Italy.

Peroxisome proliferator-activated receptor  $\alpha$  is a transcription factor belonging to the nuclear receptor superfamily with physiological functions ligand and tissue distribution dependent. A growing body of literature suggests for PPAR- $\alpha$  a pivotal role in controlling inflammatory process. More recently, it has been clearly shown that PPAR- $\alpha$  receptor can also mediate a broad spectrum of analgesic effects and that it can be considered as a pivotal target for several endogenous fatty acid ethanolamide, a new class of lipid neuromodulator. Little is known about PPAR- $\alpha$  roles in the CNS, although the localization in different areas has been reported.

We have investigated the possible role of central PPAR- $\alpha$  receptor in controlling peripheral inflammation, in the model of carrageenan-induced paw edema in mice.

The synthetic PPAR- $\alpha$  agonist, GW7647 (0.1-1 $\mu$ g i.c.v.; 30 min before carrageenan injection) reduced time dependent edema formation. This action was absent in mutant mice lacking PPAR- $\alpha$  receptor. Western blot analysis showed a down-expression of spinal PPAR- $\alpha$  receptor and an over-expression of COX-2 and iNOS in spinal cord and sciatic nerve from carrageenan-injected mice. PPAR- $\alpha$  agonist i.c.v. pre-treatment up-regulated PPAR- $\alpha$  content and reduced the expression of pro-inflammatory enzymes in a significant manner. Moreover, our data suggest that PPAR- $\alpha$  anti-inflammatory activity appears to be mediated by prevention of I $\kappa$ B- $\alpha$  degradation and NF- $\kappa$ B nuclear translocation. Taken together, these data show for the first time that PPAR- $\alpha$  activation in the CNS can control peripheral inflammation through a control of pro-inflammatory enzymes expression in the spinal cord and sciatic nerve.