Pharmacokinetic characteristics and pharmacological profile of polyethylenglicole derivatives of palmitoylethanolamide (PEA)

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N-Palmitoylethanolamide (PEA), the amide of palmitic acid and ethanolamine, has been proposed as an endogenous agonist for peroxisome proliferators-activated receptor-alpha (PPAR-alpha). PEA has been widely studied for its analgesic and anti-inflammatory effects, and its properties have been shown to be dependent on PPAR-alpha expression (Lo Verme 2006). Multiple lines of evidence suggest that PPAR-α receptors and their ligands are important modulators of the inflammatory process and they are involved in modulation of pain (Daynes and Jones, 2002, D'Agostino G, et al., 2009; Sasso et al., 2013). Our recent evidence show that PEA does not elicit anti-inflammatory effects in mutant PPAR-α null mice (PPAR α -/- mice) (LoVerme et al., 2005). Moreover, when administered in a topical formulation to inflamed mouse skin, PEA inhibits inflammation and induces the expression of PPAR-α mRNA, an effect characteristic of synthetic high-affinity PPAR-α ligands (LoVerme et al., 2005). Pro-drug technologies are commonly employed to improve the membrane permeability or solubility of drugs. The important distinction between analogs and pro-drugs is that the former are biologically active, whereas the latter require *in vivo* modification in order to elicit biological activity. In this study we used PEA and its pro-drugs (PEA -PEG1 and -PEG2), with one and two molecular of polyethylene add to PEA, to determine their efficacy on carrageenan induced paw oedema and hyperalgesia, after local application (patent n° MI2012A002127). In particular, the aim of this study is estimate an improvement of pro-drug efficacy versus reference drug. In fact, PEA -PEG1 and –PEG2, thanks to linkage of polyethylene glycol, is slowly released, evoking a longest effect, and highest skin concentration, respect to PEA. Results showed that carrageenan injection into the mice paw produced both a significant hyperalgesia as determined by a reduction in withdrawal latencies, and paw oedema determined by an increase of paw volume. PEA (1mg/paw), markedly reduced mechanical hyperalgesia and paw oedema; in particular, anti-hyperalgesic and anti-inflammatory effects were observed at 2 and 4 h following application. PEA-PEG1 treatment at equimolecular dose of PEA, showed a significant anti-hyperalgesic and anti-inflammatory activities at 6h until at 72h following local application, while no effect was observed at 2-4h. Similarly, local application of PEA-PEG2 at equimolecular dose of PEA reduced mechanical hyperalgesia and paw oedema at 48 until 96h following local application. Results obtained from in vivo experiments were in accordance with data collected from skin accumulation experiments. Collectively, these findings confirm that PEA and their pro-drugs have an anti-inflammatory and anti-hyperalgesic activities, with important difference that PEA has a rapid effect (2-4 h), whereas pro-drugs, following local application, and after 'metabolization', releases slowly PEA, producing an clear and siginificative effect until to 96h.

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