N-ARACHIDONOYL-SEROTONIN: A FATTY ACID AMIDE HYDROLASE INHIBITOR WITH ANTAGONISTIC ACTIVITY AT TRPV1 RECEPTORS AND ANALGESIC PROPERTIES IN VIVO

Palazzo Enza[1], De Petrocellis Luciano[2], Petrosino Stefania[2], Gatta Luisa[1], Guida Francesca[1], Ortar Giorgio[3], Rossi Francesco[1], Maione Sabatino[1], Di Marzo Vincenzo[2]

[1]Department of Experimental Medicine, Section of Pharmacology "L. Donatelli", Second University of Naples, via Costantinopoli 16, 80138 Naples. [2]Endocannabinoid Research Group, Institutes of Cybernetics and of Biomolecular Chemistry, CNR , Pozzuoli (Naples).[3]Dipartimento di Studi Farmaceutici, Università di Roma 'La Sapienza", Roma

N-arachidonoyl-serotonin (AA-5-HT) is a non-competitive inhibitor of fatty acid amide hydrolase (FAAH), the enzyme responsible of the hydrolysis of the endocannabinoid anandamide, and a non-competitive antagonist at rat and human transient receptor potential vanilloid-1 (TRPV1) receptors

The analgesic potential of AA-5-HT was tested in healthy rats, in rats and mice treated with formalin and in rats with chronic constriction injury of the sciatic nerve. AA-5-HT behaved as a strong analgesic in healthy rats, in rats and mice treated with formalin and in neuropathic rats. The analgesic effect of AA-5-HT was partially due to FAAH inhibition and indirect activation of cannabinoid receptors since it was reversed by AM251, a CB1 antagonist. AA-5-HT also appeared to act either via activation/desensitization of TRPV1 receptors, following elevation of AEA, or as a direct TRPV1 antagonist. Accordingly, the analgesic effect of AA-5-HT was either reversed or mimicked by capsazepine and 5'-iodo-resineferatoxin, two TRPV1 antagonists. A mechanism of action of AA-5-HT as a dual FAAH inhibitor and TRPV1 antagonist was observed particularly in mice treated with formalin, and was confirmed using equipotent analogs of AA-5-HT with activity at only one of each target.

Intra-periaqueductal grey (PAG) AA-5-HT also produced anti-nociceptive behavioural effects against several types of pro-algesic stimuli in vivo in rats. Moreover in unesthetized rats intra-PAG AA-5-HT changed rostral ventromedial medulla (RVM) activity of pro-nociceptive ON e antinociceptive OFF cells, in a way that was consistent with its analgesic effect. The effects of AA-5-HT were also in this case antagonized by AM251 but also by capsazepine, at doses devoid of any behavioural effect. Possibly due to its dual activity as a FAAH inhibitor and TRPV1 antagonist, AA-5-HT is a potent analgesic in acute and chronic peripheral pain in rodents.