

## [2003 Fall A1] Endocannabinoid analgesia in normal and neuropathic rats

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**Introduction:** Endogenous cannabinoids (CB) mediate analgesic effects and are especially effective to relieve hyperalgesic states (1). Since the use of exogenous synthetic CB agonists induces major psychotropic side effects, an alternative approach is to prevent endogenous CB degradation with the development of compounds acting as substrates for FAAH enzyme but inactive at CB receptors, by example oleoylethylamide (OEA), a new derivative of palmitoylethanolamide (2). The study intends to compare the antinociceptive effect of OEA with that of endogenous CB anandamide (AEA- a CB1 ligand) and palmitoylethanolamide (PEA - a putative CB2 ligand), using both normal and neuropathic animals.

**Material and Methods:** After animal care committee approval, adult male Wistar rats underwent sham surgery (controls; n=18) or partial ligation of one sciatic nerve (PSN ; n=24) under halothane anesthesia. Ten to twelve weeks after surgery, nociceptive threshold was assessed by latency to withdraw the hindpaw from a radiant heat stimulus (PWL, cutoff 20.48 sec). Results of both hindpaws were pooled together in C and also in PSNL rats in whom PWL were equally reduced on both sides (3). After PWL baseline, animals received various doses of IP AEA (10 - 30 mg/kg), PEA (10 - 30 mg/kg) and OEA (10 - 30 mg/kg) to determine drugs ED50 by linear regression. Reversal of 65% analgesic effect of equivalent doses of PEA and OEA was then evaluated following IP pretreatment (1 mg/kg) with CB1 antagonist SR141716 or CB2 antagonist SR144528. Statistical analysis used raw data and ANOVA tests. Results are mean±SD.

**Results:** Baseline PWL was  $12.6 \pm 1.1$  sec and  $10.0 \pm 0.6$  sec respectively in C and PSNL rats ( $P = 0.006$ ). ED50 (mg/kg) was in C and PSNL: 25.6 and 21.4 for AEA, 9.5 and 17.6 for OEA and 9.3 and 14.5 for PEA. In normal rats, OEA pretreatment with antiCB1 reduced analgesia from 65% MPE to  $-5 \pm 8$  % ( $P = 0.0005$ ) and with antiCB2 to  $36 \pm 16$  % ( $P = 0.0035$ ) whereas pretreatment did not modify PEA analgesia ( $53 \pm 2$  % after antiCB1 and  $54 \pm 11$  % after antiCB2). In neuropathic rats, 65 % MPE of OEA was decreased to  $45 \pm 11$  % ( $P = 0.05$ ) with antiCB1 pretreatment but not modified by antiCB2 ( $79 \pm 11$  % MPE;  $P = 0.39$ ). In these animals, 65 % MPE of PEA was reversed with antiCB2 pretreatment ( $34 \pm 14$  %;  $P = 0.017$ ) but not with antiCB1 ( $55 \pm 24$  %;  $P = 0.81$ ). OEA injection resulted into less excitability than administration of PEA and AEA.

**Conclusion:** In normal rats, OEA analgesic effect is equivalent to PEA, superior to AEA, and especially mediated at CB1 receptors. In neuropathic rats, PEA is more effective (than OEA and AEA) to relieve established thermal hyperalgesia, an effect mediated at CB2 receptors, as it was previously reported in different hyperalgesic models (1). Hence, the analgesic effect of OEA seems to differ from that of PEA and to result from its interference with the inactivation of endogenous CB, enhancing their action at CB1 receptors according to the underlying physiological conditions.

**References:** (1) Jaggar et al. Pain 1998 ; 76 : 189-199. (2) Jonsson K-O et al. Br J Pharmacol 2001 ; 133: 1263-75. (3) Takaishi et al. Pain 1996 ; 66 : 297-306.