**P026**

**Spinal Endocannabinoid/Endovanilloid System As A Target For Suppression Of Neuropathic Pain In**

**Rats**

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Neuropathic pain is one of the main challenges of pain therapy and due to its complex etiology the current treatments have limited effectiveness. Cannabinoids and more importantly endocannabinoids have the potential to address this unmet need. Anandamide (AEA), the first identified endocannabinoid, produces most of the pharmacological effects by activating cannabinoid 1 receptors (CB1). AEA activates also TRPV1 receptor, thus can be considered an endovanilloid as well. Current studies emphasize targeting endocannabinoids, rather than the cannabinoids receptors, as an alternative approach to achieve analgesia. This approach is limited by rapid termination of AEA's actions by fatty acid amide hydrolase (FAAH), which can be omitted by FAHH inhibitor (URB597) administration. We tested the hypothesis postulated by Petrosino S et al. (Neuropharm 52:415,2007) that up-regulated AEA levels might inhibit pain and/or delay the development of neuropathic pain symptoms.

Male Wistar rats (n=8-10 per group) were implanted with an intrathecal (i.t.) catheter according to Yaksh TL & Rudy TA (Science 192:1357,1976). Animals were subsequently subjected to sciatic nerve injury (CCI) (Bennet GJ & Xie YK, Pain 1:87,1988). We tested the effects of single and prolonged pharmacological inhibition of FAAH (URB597 100µg/10µl i.t.) on the development of hyperalgesia 1-14 days after CCI. Western Blot analysis of NAPE-PLD and FAAH were also performed. Results were evaluated by one-way analysis of variance (ANOVA) and those with p-value<0.05 were considered significant.

Already at day two after injury CCI rats developed hyperalgesia, that gradually increased until day 14. A single dose of URB597 administered preemptively before CCI did not prevent and/or attenuate the development of neuropathic pain. Chronic administration of URB597 started before nerve injury and continued for 3 days after CCI significantly prevented the development of neuropathic pain. These group showed longer tests' latency times even 12 days post-injury when compared to vehicle-treated CCI rats. URB597 delayed progression of neuropathic pain via both spinal CB1 and TRPV1 receptors, depending on the stimulus modality.

As demonstrated in authors' other study (Starowicz K et al., Neuropharm 62:1746; Petrosino S et al., Neuropharm;52:415-22, 2007) tissue concentrations of AEA in the spinal cord become up-regulated as an adaptive response to neuropathic pain aimed at counteracting pain transmission. The CCI-induced upregulation of AEA levels in the spinal cord is associated with decrease of its anabolic enzyme (NAPE-PLD), possibly as an adaptive response to its elevated levels and a concomitant decrease with its catabolic enzyme FAAH. Selective pharmacological manipulation of FAAH inhibition led to a further decrease in its spinal cord levels. A counteracting reaction of NAPE-PLD was observed possibly aimed to restore physiological balance in AEA's metabolic enzymes. As initially pharmacological inhibition of FAAH was shown to delay neuropathic pain development in CCI rats. This may, via accumulation of AEA, lead to the activation of CB1 receptors as well as activation/desensitisation of TRPV1. These data provide further evidence on the complexity of cross-talk between CB1 and TRPV1 in the control of ascending pain pathways and in the development of CCI-induced hyperalgesia. [Supported by LIDER/29/60/L-2/10/NCBiR/2011]