**P106**

## ANTI-HYPERALGESIC EFFECTS OF ARN_077, AN IRREVERSIBLE INHIBITOR OF N-ACYLETHANOLAMINE-HYDROLYZING ACID AMIDASE (NAAA), IN TWO MURINE MODELS OF PAIN

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Ethanolamides of different long-chain fatty acids constitute a class of endogenous lipid molecules generally called N-acylethanolamines (NAEs). They contain N-arachidonoylethanolamide (anandamide), N-palmitoylethanolamide, and N-oleoylethanolamide, which receive considerable attention because of their actions as an endogenous cannabinoid receptor ligand (endocannabinoid), an anti-inflammatory and an appetite-suppressing substance, respectively. Identification of their biosynthetic routes and molecular characterization of the enzymes involved in the biosynthetis and degradation are essential for better understanding of physiological importance of NAEs. Until 2001, only Fatty Acid Amide Hydrolase (FAAH) was known as the major enzyme involved in the NAEs degradation. Subsequently, Ueda et al. (2001) found in rat tissues another enzyme involved in the NAEs degradation, NAE-hydrolyzing acid amidase (NAAA) (1) and established that this enzyme had no homology to FAAH (2). Later studies revealed that NAAA is one of lysosomal hydrolases (3) and may be a new target for the development of therapeutic drugs. The aim of the present study is to evaluate the effect of a new irreversible inhibitor of NAAA, ARN077, in two murine model of persistent and chronic pain. A single topical administration of ARN077 (1-30%) shows a significant dose and time-depending anti-edematogenic and anti-hyperalgesic effects in the model of carrageenan-induced paw edema or chronic constriction injury (CCI) in mice. The involvement of PPAR-alpha, CB1 and CB2 receptors was also investigated. Our pharmacological experiments with GW 6471, AM 251 and AM 630 supported the hypothesis of an increase of PEA levels due to a inhibiton of NAAA and the involvement of PPAR-α receptors. Our results start to add futher support to better understand the pharmacological profile of a new NAAA inhibitor. Data (n = 6 for each group) obtained in the carrageenan and CCI models were compared using two-way analysis of variance (ANOVA) followed by Bonferroni's test for multiple comparisons.

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