

INHIBITION OF PEA DEGRADATION VIA NAAA BLOCKADE MODULATES MIGRAINE-RELATED PATHWAYS WITHOUT REVERSED TRIGEMINAL HYPERALGESIA IN FEMALE RATS IN THE NTG-BASED MIGRAINE MODEL

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Background. Increasing evidence supports the involvement of the endocannabinoid system (ECS) and related lipid mediators in migraine pathophysiology. Palmitoylethanolamide (PEA) is an endocannabinoid-like lipid with anti-inflammatory and analgesic effects, acting predominantly through PPAR-α receptors. Its bioavailability is primarily regulated by enzymatic degradation mediated by N-acylethanolamine acid amidase (NAAA). NAAA inhibition may represent a strategy to enhance endogenous PEA signaling and counteract migraine-related neuroinflammatory and nociceptive mechanisms. Here, we assessed the effects of the selective NAAA inhibitor ARN726 on trigeminal hyperalgesia in the nitroglycerin (NTG) migraine model in female rats and investigated its effects on inflammatory and endocannabinoid-related pathways, and on CGRP levels in migraine-relevant areas of the nervous system.

Methods. Female Sprague-Dawley rats (170–200 g) received NTG (10 mg/kg, i.p.) or vehicle 4h before the orofacial formalin test. ARN726 (3 mg/kg, i.p.) or vehicle was administered 2 h before behavioral testing. Gene expression of inflammatory mediators was analyzed in the medulla, whereas the ECS-related components were assessed in the medulla and TG by real-time PCR. In a separate cohort of animals, CGRP levels were quantified in the cervical spinal cord, medulla and TG by ELISA.

Results. The NTG-induced trigeminal hyperalgesia was not reversed by ARN726. In the medulla, NTG increased IL-1β and IL-6, while reducing IL-4 expression, whereas ARN726 selectively increased IL-4 compared with NTG-treated rats. ARN726 also reduced NAAA expression and increased PPAR-α expression in the medulla relative to both control and NTG groups. In the TG, NTG increased FAAH and PPAR-α expression compared with controls, whereas ARN726 reversed these changes. Additionally, ARN726 significantly reduced TRPV1, NAPE-PLD, and NAAA expression compared with both NTG and control groups. Notably, NTG did not alter basal CGRP levels in any region, whereas ARN726 significantly reduced CGRP levels in the cervical spinal cord and increased it in the medulla.

Conclusions. In a migraine specific animal model, the inhibition of PEA degradation in female rats induced a wide range of effects over mediators of inflammation, nociception and endocannabinoid function, without interfering with trigeminal hyperalgesia. Further studies are needed to optimize the targeting of the NAAA–PEA axis and to clarify its therapeutic potential in female models of migraine.