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Benefits of The ALIAmide Palmitoyl-Glucosamine Co-Micronized with Curcumin for Osteoarthritis Pain: A Preclinical Study

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Abstract : Osteoarthritis (OA) is one of the most common chronic pain conditions in dogs and cats. OA pain is currently viewed as a mixed phenomenon involving both inflammatory and neuropathic mechanisms at the peripheral (joint) and central (spinal and supraspinal) levels. Oxidative stress has been implicated in OA pain. Although nonsteroidal anti-inflammatory drugs are commonly prescribed for OA pain, they should be used with caution in pets because of adverse effects in the long term and controversial efficacy on neuropathic pain. An unmet need remains for safe and effective long-term treatments for OA pain. Palmitoyl-glucosamine (PGA) is an analogue of the ALIAamide palmitoylethanolamide, i.e., a body's own endocannabinoid-like compound playing a sentinel role in nociception. PGA, especially in the micronized formulation, was shown safe and effective in OA pain. The aim of this study was to investigate the effect of a co-micronized formulation of PGA with the natural antioxidant curcumin (PGA-cur) on OA pain. Ten Sprague-Dawley male rats were used for each treatment group. The University of Messina Review Board for the care and use of animals authorized the study. On day 0, rats were anesthetized (5.0% isoflurane in 100% O2) and received intra-articular injection of MIA (3 mg in 25 µl saline) in the right knee joint, with the left being injected an equal volume of saline. Starting the third day after MIA injection, treatments were administered orally three times per week for 21 days, at the following doses: PGA 20 mg/kg, curcumin 10 mg/kg, PGA-cur (2:1 ratio) 30 mg/kg. On day 0 and 3, 7, 14 and 21 days post-injection, mechanical allodynia was measured using a dynamic plantar Von Frey hair aesthesiometer and expressed as paw withdrawal threshold (PWT) and latency (PWL). Motor functional recovery of the rear limb was evaluated on the same time points by walking track analysis using the sciatic functional index. On day 21 post-MIA injection, the concentration of the following inflammatory and nociceptive mediators was measured in serum using commercial ELISA kits: tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), nerve growth factor (NGF) and matrix metalloproteinase-1-3-9 (MMP-1, MMP-3, MMP-9). The results were analyzed by ANOVA followed by Bonferroni post-hoc test for multiple comparisons. Micronized PGA reduced neuropathic pain, as shown by the significant higher PWT and PWL values compared to vehicle group ($p < 0.0001$ for all the evaluated time points). The effect of PGA-cur was superior at all time points ($p < 0.005$). PGA-cur restored motor function already on day 14 ($p < 0.005$), while micronized PGA was effective a week later (D21). MIA-induced increase in the serum levels of all the investigated mediators was inhibited by PGA-cur ($p < 0.01$). PGA was also effective, except on IL-1 and MMP-3. Curcumin alone was inactive in all the experiments at any time point. The encouraging results suggest that PGA-cur may represent a valuable option in OA pain management and warrant further confirmation in well-powered clinical trials.

Keywords : ALIAmides, curcumin, osteoarthritis, palmitoyl-glucosamine
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