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Canephron® N reduces pain in experimental cystitis and prostatitis putatively by inhibition of PGE2 production

Nausch B.[1], Koeberle A.[2], Werz O.[2], Ammendola A.[1], Künstle G.[1]

[1]Bionorica SE, Preclinical R&D, Neumarkt, Germany, [2]Friedrich Schiller University Jena, Institute of Pharmacy, Jena, Germany

INTRODUCTION & OBJECTIVES: Inflammation and increased levels of Prostaglandin E_2 (PGE2) contribute to the most bothersome symptom of cystitis and prostatitis: pain. The massive production of PGE_2 during inflammation depends on the concerted action of Cyclooxygenase (COX)-2 and microsomal Prostaglandin E_2 Synthase (mPGES)-1.

Here we investigated the effects of the herbal medicinal product Canephron® N (Can N) on pain using the formalin test and experimental cystitis as well as prostatitis. In addition, we investigated its effects on PGE_2 production, a major player in inflammatory pain.

MATERIAL & METHODS: Prostatitis was induced in rats by intraprostatic injection of carrageenan and nociceptive threshold and score were determined using von Frey filaments. Can N was administered per os (p.o.) at 666 mg/kg twice a day. Cystitis was induced in rats by intraperitoneal injection of cyclophosphamide and nociceptive parameters were determined using von Frey filaments. Can N (6.6, 66, or 666 mg/kg) was administered p.o. twice a day. Formalin test: Pain responses were observed immediately and 20 minutes after injection of 5% formalin solution into the hind paw of rats. Can N was administered p.o. 120 minutes before formalin injection at doses of 6.6, 66, and 666 mg/kg. mPGES-1 activity, cell-free: The mPGES-1 substrate PGH_2 was added to mPGES-1-containing membrane fractions of IL-1β-stimulated A549 cells in presence and absence of Can N. The product PGE_2 was measured by high performance liquid chromatography (HPLC). COX-2 activity, cell-free: Activity of human recombinant COX-2 was determined in presence and absence of Can N by measuring the product 12-hydroxy-heptadecatrienoic acid (12-HHT) by HPLC. PGE_2 release in vitro: freshly isolated human monocytes were stimulated by LPS in presence and absence of Can N and released PGE_2 was measured by ELISA.

RESULTS: Can N normalized nociceptive threshold and score in experimental cystitis, even at a dose corresponding to less than the recommended human daily dose, i.e. 6.6 mg/kg, and had similar effects in experimental prostatitis. In contrast, Can N had no effect in the formalin test, indicating a lack of direct analgesic effects. Can N inhibited the enzyme mPGES-1 (IC_{50} = 65 µg/ml) but not COX-2 and prevented PGE_2 release from freshly isolated and activated human monocytes in vitro (IC_{50} = 80 µg/ml).

CONCLUSIONS: Inflammation, pain and increased levels of PGE_2, a key player in inflammatory pain, are integral parts of cystitis and prostatitis. Can N did not produce analgesic effects in the formalin test, suggesting that the normalization of pain responses in cystitis and prostatitis is rather due to anti-inflammatory effects, i.e. inhibition of PGE_2 release. In conclusion, Can N interferes with mPGES-1 and shows the potential to reduce pain in cystitis and prostatitis by virtue of anti-inflammatory effects. Thus, Can N adds a novel and promising treatment option for prostatitis in addition to its long standing use in cystitis.