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FAAH INHIBITION REVERSES BLADDER REFLEX ACTIVITY AND REDUCES BLADDER HYPERALGESIA INDUCED BY CYSTITIS THROUGH A CB1-MEDIATED MECHANISM.

Hypothesis / aims of study

The endocannabinoid modulation has emerged as new option for treatment of several bladder dysfunctions. When compared cannabinoid agonists, the modulation of endocanabinoids offer the advantage of activating the cannabinoid system without developing undesirable psychotropic side-effects [1].

Increase of endocannabinoid agents as anandamide (AEA) was shown to occur after the inhibition of fatty acid amide hydrolase (FAAH), the key enzyme in AEA degradation. Therefore, in this work, we intend to study the effect of a FAAH antagonist to treat inflammation-induced hyperalgesia and bladder reflex overactivity and to determine the involvement of the cannabinoid receptors triggered by anandamide.

Study design, materials and methods

Adult female rats were divided in 2 groups. In one, bladder inflammation was induced by intravesical instillation of 2 mg/ml lipopolysaccharide (LPS), for 1h, 24h prior to experiment (LPS inflamed group). In a second group (control group), sham inflammation was reproduced with saline instillation. All animals were anaesthetised with urethane (1.2 g/kg subcutaneously), submitted to cystometric analysis, with saline infusion at 6 ml/h, while cystometric traces were recorded. Afterwards, urinary bladders were harvested, immersion fixed, stained for Hematoxylin-eosin and analysed to confirm histological signs of cystitis.

Both inflamed and control animals intravenously received URB937 (FAAH antagonist) during cystometry, in doses of 0.01, 0.1, 1 and 5 microM (cumulative), with 10 minutes interval.

Another set of inflamed and control animals intravenously received URB937 1 microM (the most effective dose) during cystometry. Two hours after URB937 administration, animals were perfused fixed, L6 spinal segment harvested and immunoreacted against Fos protein. The number of cells expressing Fos/slide was counted.

A third set of control and inflamed animals intravenously received vehicle, MJ15 (CB1 antagonist)+URB937 1 microM or SR144528 (CB2antagonist)+URB937 1 microM, during cystometry.

Results

The frequency of reflex bladder contractions in sham rats was 0.5±0.1 bladder contractions/minute at baseline and it was not changed with by URB937 administration at any of the doses tested. In inflamed rats frequency of bladder contractions at baseline was 2.1±0.6 bladder contractions/minute ($p<0.01$). URB937 treatment decreased bladder frequency, in a dose dependent manner (1.7±0.6 and 1.2±0.6 bladder contractions, for 0.01 and 0.1 microM, respectively). At dose of 1 microM, URB937 completely reversed inflammation-induced bladder hyperflexia (0.8±0.2 bladder contractions/minute).

Control animals presented 9 Fos-expressing cells in L6 spinal cord segment. LPS inflamed animals presented a mean number of 42 Fos-expressing cells in L6 spinal cord segment. The mean number of Fos-expressing cells from LPS inflamed animals that received 1 microM URB937 was 22.

Injection of SR144528, the CB2 antagonist, had no effect on bladder reflex contractions of control animals. Furthermore, SR144528 was unable to reverse 1 microM URB937-mediated decrease in frequency of LPS-inflamed animals.

Treatment of control animals with MJ15, the CB1 antagonist, did not change bladder reflex activity. In LPS-inflamed animals, MJ15 completely blocked the decrease of bladder reflex activity induced by 1 microM URB937 (1.3±0.1 bladder contraction/minute prior and after to URB937+MJ15).

Interpretation of results

Intravenous FAAH inhibitor URB937 reverses bladder hyperreflexia in a dose dependent manner up to 1 microM doses. At this dose, the decrease in the number of spinal Fos-expressing cells induced by URB937 indicates that the blockade of FAAH might have bladder analgesic effects.

Since CB1 antagonist, but not CB2 antagonist, reverses the effect of URB937, we concluded that the activation of the cannabinoid system induced by AEA was mediated by CB1 receptor.

Concluding message

These results may be highly relevant for the clinical use FAAH inhibitors to treat bladder pain and hyperactivity associated with bladder inflammation.

References

1. Curr Opin Chem Biol. 7(4):469-75.2003

Disclosures

Funding: Ana Charrua is funded by SFRH/BPD/68716/2010 **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** European Communities Council Directive of 24 November 1986 (86/609/EEC)