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EFFECTS OF IP751, AJULEMIC ACID, ON BLADDER OVERACTIVITY INDUCED BY BLADDER IRRITATION IN THE RAT

Hypothesis / aims of study
Ajulemic acid (IP751) is a potent analog of tetrahydrocannabinol (THC)-11-oic acid, which is a major metabolite of THC, the principal psychotropic constituent of Cannabis. IP751 reportedly shows potent anti-inflammatory activity and is a powerful analgesic agent although the underlying mechanisms are still unknown. Thus, we hypothesized that IP751 is effective to suppress bladder overactivity and bladder pain responses in bladder hypersensitive disorders such as interstitial cystitis. Therefore, the present study was performed to investigate the effects of IP751 on bladder overactivity induced by acute and subacute bladder irritation in rats.

Study design, materials and methods
Cystometrograms (CMGs) were performed under urethane anesthesia using a catheter inserted into the bladder through the bladder dome via a midline abdominal incision. Saline was infused at a rate of 0.04 ml/min to elicit repetitive bladder contractions. Effects of intravenous (i.v.) injection of IP751 on bladder overactivity induced by either intravesical administration of acetic acid solution or one day treatment with cyclophosphamide were investigated.

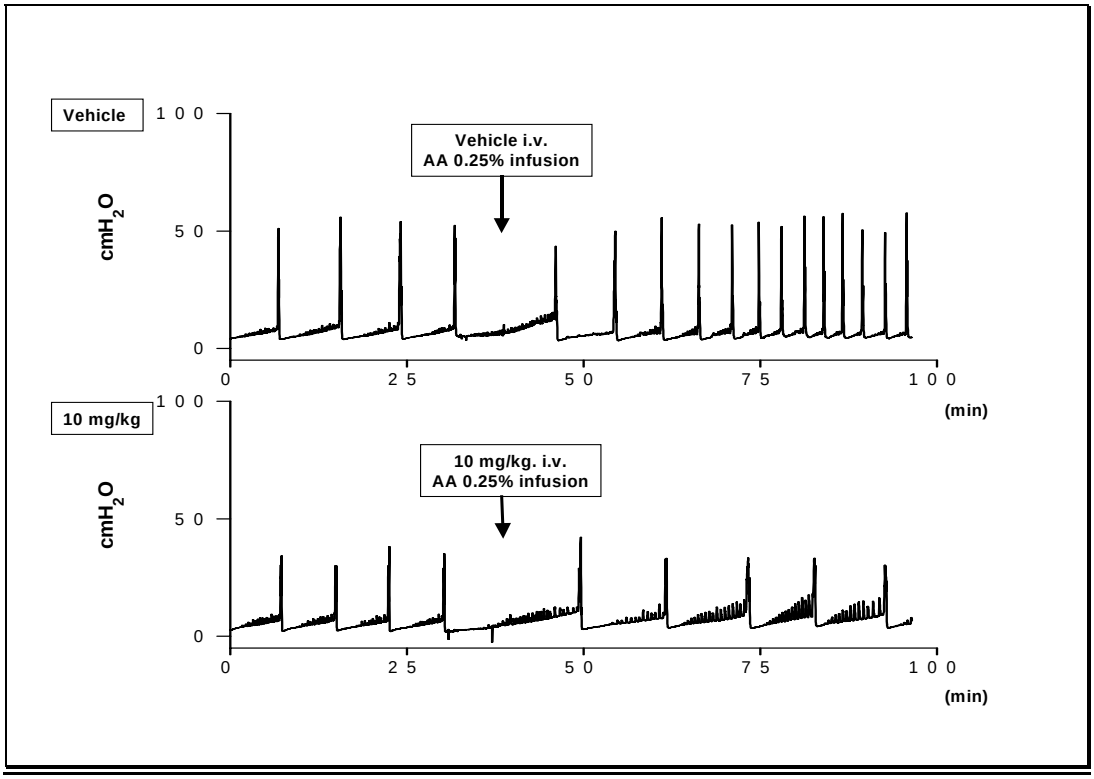
1. Acute bladder irritation by acetic acid infusion: Control CMGs were recorded for 1 to 2 hours prior to drug administration. IP751 or vehicle (30% Cremophor EL in saline) was administrated intravenously when starting infusion of acetic acid solution (0.25%) into the bladder. Changes in cystometric parameters such as intercontraction intervals (ICIs), maximum voiding pressure (MVP), pressure threshold (PT) and baseline pressure (BP) were evaluated before and after i.v. administration of IP751 or vehicle.

2. Subacute bladder irritation by cyclophosphamide: One day after intraperitoneal injection of cyclophosphamide (CYP 150 mg/kg), control CMGs were recorded for 1 to 2 hour prior to i.v. administration of IP751 or vehicle. Following administration of IP751, changes in cystometric parameters such as ICIs, MVP, PT and BP were recorded to evaluate the effects of IP751 on cyclophosphamide-induced bladder overactivity.

Results
1. Acetic acid infusion: In the vehicle group, 0.25% acetic acid infusion induced significant bladder overactivity evidenced by a reduction in ICIs to 42.9 % of the control value. This reduction in ICIs was suppressed by IP751 at a dose of 10 mg/kg to 112.4% of the control value ($P<0.05$, $n=6$), but not by IP751 at doses of 1mg/kg and 3 mg/kg (45.2% and 51.1% of the control value, respectively). IP751 at a dose of 10 mg/kg also increased the pressure threshold to 127.2 % of the control value while vehicle, 1 mg/kg or 3 mg/kg of IP751 did not have such increases (87.1%, 74.1%, 94.1% of the control value, respectively). There were no significant changes in MVP and BP.

2. Cyclophosphamide*:* Bladder overactivity indicated by significant ICI reductions was observed one day after CYP injection. Administration of IP751 at a dose of 10 mg/kg (i.v.) significantly suppressed CYP-induced bladder overactivity as evidenced by the increment of ICIs to 5.14 min from control value (3.65 min) while vehicle did not alter ICIs (3.89 vs. 3.94 min) in CYP-treated rats. There are no significant changes in MVP, PT and BP after IP751 administration.

Figure 1: Effects of IP751 on acetic acid induced bladder overactivity



Interpretation of results

IP751 at a dose of 10mg/kg significantly suppressed bladder overactivity induced by acetic acid infusion (acute model) and administration of cyclophosphamide (subacute model) without affecting bladder contractility.

Concluding message

These results indicate that IP751 can suppress bladder nociceptive responses induced by bladder irritation probably due to suppression of bladder sensory activity. Thus IP751 could be effective for the treatment of pain and urinary frequency symptoms in patients with painful bladder syndrome/interstitial cystitis.

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