

Bladder and Urethra: Anatomy, Physiology & Pharmacology
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**EFFECTS OF IP751, AJULEMIC ACID, ON BLADDER OVERACTIVITY
INDUCED BY BLADDER IRRITATION IN THE RAT**

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Introduction and Objective: Ajulemic acid (IP-751) 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. Thus, we hypothesized that IP751 is effective to suppress urinary frequency and bladder pain responses in bladder hypersensitive disorders such as interstitial cystitis. Therefore, the present study was performed to investigate the effects of IP-751 on urinary frequency induced by acute and subacute bladder irritation in rats. **Methods:** Continuous cystometrograms (infusion rate: 0.04 ml/min) was performed in order to evaluate the effect of intravenous injection of IP751 with or without CB1 antagonist (AM251) or CB2 antagonist (AM630) on bladder function in urethane-anesthetized rats. The effect of IP-751 was then investigated in rats with C-fiber desensitization induced by capsaicin pretreatment, or in rats with urinary frequency induced by intravesical infusion with 0.25 % acetic acid or cyclophosphamide (CYP)(150 mg/kg i.p., 48 hr prior to cystometrograms). **Results:** **1. Acetic acid infusion:** In the vehicle group, 0.25% acetic acid infusion induced significant urinary frequency evidenced by a reduction in ICIs. This reduction in ICIs was suppressed by IP-751(10 mg/kg). IP-751 (10 mg/kg) also increased pressure threshold(PT). **2. CYP:** Urinary frequency indicated by significant ICIs reductions was observed 48hours after CYP injection. Administration of IP-751(10 mg/kg) significantly suppressed CYP-induced urinary frequency as evidenced by the increment of ICIs. **3. Antagonist treatments:** When IP-751 (10mg/kg) was injected in control rats, ICIs and PT were increased. However, when the AM251(3mg/kg) , but not the AM630, was administered prior to IP-751 (10mg/kg), IP-751-induced increases in ICIs and PT was prevented. In addition, C-fiber desensitization by capsaicin pretreatment also prevented IP-751-induced increases in ICIs and PT. **Conclusions:** These results indicate that IP-751 can suppress bladder nociceptive responses induced by bladder irritation, and that the inhibitory effects of IP-751 on bladder activity is mediated at least in part by CB1 receptors located on C-fiber afferents. Thus IP-751, ajulemic acid, could be effective for the treatment of pain and urinary frequency symptoms in patients with painful bladder syndrome/interstitial cystitis.

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