

EFFECT OF THE 5-HT_{1A} RECEPTOR ANTAGONIST REC 27/0262 ON CYSTOMETRY IN CONSCIOUS RATS AND DOGS

Hypothesis / aims of study

Experimental studies in animals have revealed that reflex circuits involved in voiding function exhibit a dense serotonergic innervation, multiple 5-HT receptors, and sensitivity to 5-HT receptor agonists and antagonists, supporting the use of serotonergic drugs for the treatment of detrusor overactivity and urinary incontinence (1).

Rec 27/0262 (cyclohexyl {2-[4-(1H-indol-4-yl)-piperazin-1-ylmethyl]-3,4-dihydro-2H-quinolin-1-yl} methanone) is a novel tetrahydroquinoline derivative endowed with 5-HT_{1A} receptors antagonistic activity. The overall data indicate that 5-HT_{1A} receptors have excitatory physiological role in the control of micturition in the rat, however data in cats using 8-OH-DPAT and WAY 100635 suggest the opposite, in that activation of these receptors is inhibitory to the bladder (2). Owing to these findings we decided to test the effect of Rec 27/0262 in cystometrographic models in conscious rats and dogs.

Study design, materials and methods

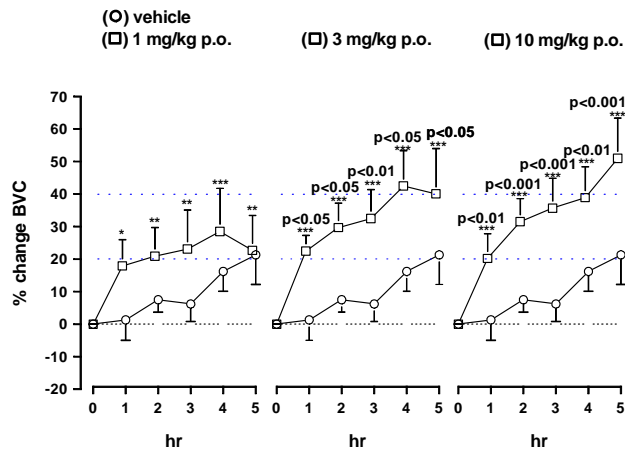
Cystometry in conscious rats was performed one day after catheter (Portex, ID 0.58 mm, OD 0.96 mm) implant in the bladder dome. On the day of the experiment, the rats were placed in Bollman's cages; the free tip of the cannula was connected by a T-shape tube to a pressure transducer and to a peristaltic pump for a continuous infusion of warm saline solution (37° C) into the urinary bladder, at the constant rate of 0.1 ml/min. Two urodynamic parameters from the cystometrogram were evaluated: bladder volume capacity (BVC) and micturition pressure (MP). Basal BVC and MP were evaluated as mean values from the cystometrograms recorded in a 30 minute interval prior to treatment. Then, bladder infusion was stopped, animals were treated orally with the test compound or vehicle and, after restarting bladder filling, changes in BVC and MP were evaluated hourly for 5 hr.

Cystometry in conscious dogs was performed according to the method reported by Yamamoto et al. (3) with some modifications. Male beagle dogs (weighing 10-12 kg) were anesthetized with sodium pentobarbital (35 mg/kg i.v.). Under sterile condition the abdomen was opened through a midline laparotomy and the bladder was exposed. The tip a 12 F double lumen catheter for cystomanometry was introduced in the bladder dome and anchored with a silk suture. The catheter was threaded subcutaneously on the left flank and the other side exteriorized and sutured on the back. Following the surgical intervention, a 1-week period was allowed for healing prior to urodynamic studies. The animals were placed in a semi-restraining sling for cystometrographic recording. The catheter contained two separate polyethylene tubes that were connected to a pump for saline infusion and to a pressure transducer, respectively. Saline (37°C) was infused into the bladder at a rate of 5 ml/min, and intravesical pressure was recorded continuously on a polygraph system. The following parameters were evaluated: BVC and MP. After a basal period in which the cystometrogram became stable the test compound or vehicle were administered orally and changes in BVC and MP were evaluated hourly for 2 hr.

Results

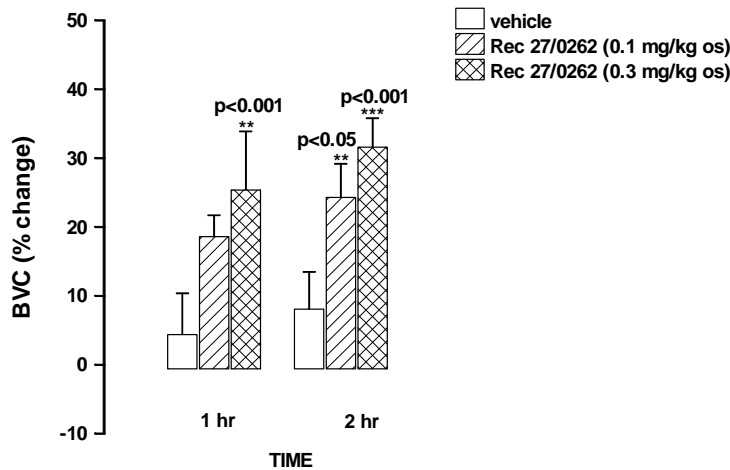
In conscious constrained rats with bladder continuously filled with saline, Rec 27/0262 induced a significant increase of BVC (in comparison with a matched control group treated with methocel) starting from the dose of 1 mg/kg (Fig.1). No significant effects on bladder contractility were observed (data not shown).

Fig. 1



Similarly, oral administration of 0.1 and 0.3 mg/kg of Rec 27/0262 in dogs dose-dependently increased BVC (Fig. 2) without affecting bladder contractility (data not shown).

Fig. 2



Interpretation of results

The present results show the excellent activity on BVC of Rec 27/0262 in the rat, confirming the positive effect of 5-HT_{1A} antagonists in this species. No effects on MP were recorded. The molecule showed the same behaviour in the dog.

Concluding message

By the use of a potent 5-HT_{1A} antagonist, the serotonergic control of micturition reflex has been shown to be similar in rats and dogs, where blockade of this receptor subtype increases the BVC, without significant effect on the MP.

References

- 1) Br J Pharmacol (2006) 147 (2); S120-S131.
- 2) Brain Res (2002) 946; 290–297.
- 3) J Urol (1995) 154; 2174-2178.

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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by EEC Council Directive 86/609