

CHARACTERIZATION OF MUSCARINIC RECEPTOR BINDING OF FESOTERODINE AFTER ORAL ADMINISTRATION IN RATS

Hypothesis / aims of study

Fesoterodine is a relatively novel antimuscarinic agent for the treatment of overactive bladder (OAB) [1]. When administered orally, fesoterodine is rapidly and extensively converted to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), which is also an active metabolite of tolterodine [2]. Our recent study with radioligand binding assay has shown that fesoterodine and 5-HMT have the tissue selectivity for the urinary bladder over parotid gland in human [3]. Furthermore, the intravesical injection of 5-HMT in rats bound the pharmacologically relevant muscarinic receptors in the bladder urothelium and detrusor muscles. Under the clinical setting, oral administration of fesoterodine is useful to treat urinary dysfunction in patients with OAB. Therefore, the current study aimed to characterize the *in vivo* muscarinic receptor binding by measuring muscarinic receptor binding in several tissues of rats after the oral administration of fesoterodine, .

Study design, materials and methods

The binding assay of muscarinic receptors in rat tissues was performed by radioligand binding assay using [N-methyl-³H]scopolamine methyl chloride ([³H]NMS) as selective muscarinic receptor radioligand. At 0.5, 2, 6 and 12 h after the oral administration of fesoterodine at doses of 3 and 10 mg/kg, muscarinic receptors in the homogenates of rat tissues (bladder, submaxillary gland, colon, heart, lung, cerebral cortex) were monitored by measuring specific [³H]NMS binding, and binding parameters of apparent dissociation constant (K_d) and maximal number of binding sites (B_{max}) for [³H]NMS were estimated using Graph Pad Prism.

Results

The oral administration of fesoterodine at the doses of 3 and 10 mg/kg dose-dependently increased the K_d values for [³H]NMS in the bladder, submaxillary gland, heart and lung, but not in the colon and cerebral cortex, with little effect on the B_{max} values (Fig. 1). The muscarinic receptor binding activity (significant enhancement of K_d) by orally administered fesoterodine in the bladder was of longer duration than that in other tissues as shown by 6 h (3 mg/kg)- and 12 h (10 mg/kg)-duration (Fig. 1). These data indicate that oral fesoterodine significantly binds to muscarinic receptors in rat tissues with bladder selectivity. Furthermore, interestingly, there was little muscarinic receptor binding activity in the colon and cerebral cortex of rats after oral administration of fesoterodine at the doses of 3 and 10 mg/kg.

Interpretation of results

These data indicate that orally administered fesoterodine significantly binds to muscarinic receptors in rat tissues with bladder selectivity. Furthermore, the binding activity of fesoterodine to the bladder receptors is relatively longer lasting compared with other tissues. We have previously shown that the excreted 5-HMT in the urine may be pharmacologically relevant, based on the direct binding of muscarinic receptors in the bladder of rats. In fact, 5-HMT showed extremely high affinity to muscarinic receptors in the urothelium and detrusor muscle of rats, and the intravesically instilled 5-HMT bound significantly to these muscarinic receptors. Pharmacologically significant amount (16%) of 5-HMT is excreted in urine of human taking clinical dose (4, 8 mg) of fesoterodine. Taken together, 5-HMT excreted in the urine, may bind significantly to bladder muscarinic receptors, thereby contributing to the bladder selectivity of oral fesoterodine. Also, it is notable that the fesoterodine administration at the pharmacological doses in rats exerted little binding activity of muscarinic receptors in the colon and cerebral cortex, suggesting less side-effects on these organs.

Concluding message

The current data indicate that oral fesoterodine significantly binds to muscarinic receptors in rat tissues with bladder selectivity. Furthermore, notably, the muscarinic receptor binding activity of fesoterodine in the bladder was relatively longer-lasting compared with other tissues.

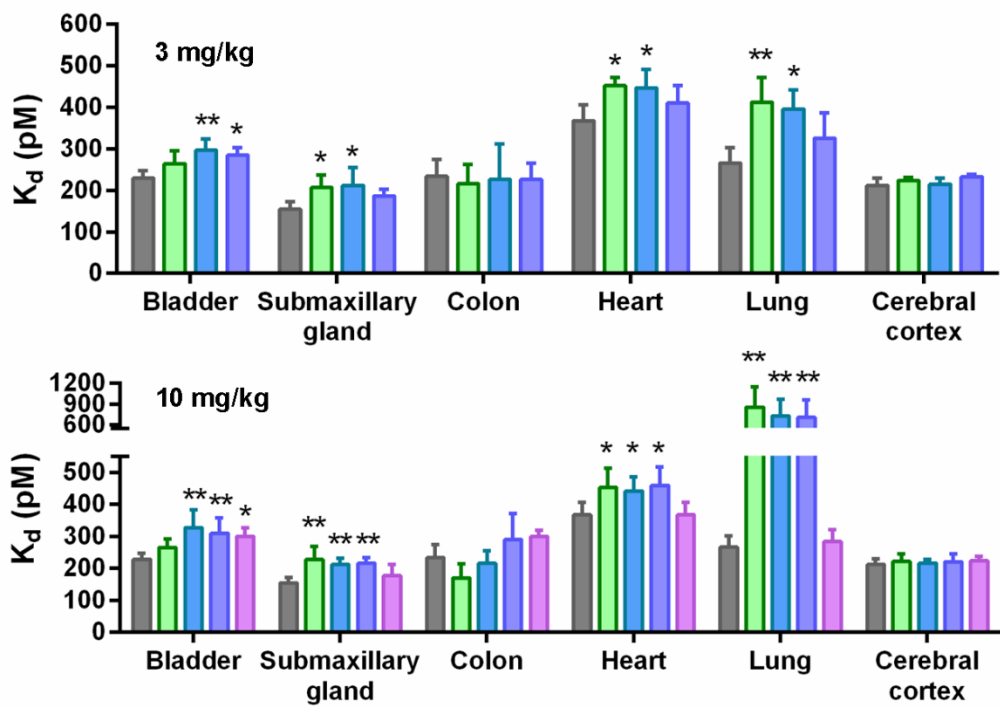


Fig. 1. Time course of muscarinic receptor binding activity (significant enhancement of K_d increase of specific [3 H]NMS binding) of orally administered fesoterodine in rat tissues at 0.5, 2, 6, and 12 h after the administration.

References

- 1 Expert Opin Pharmacother 9: 1787-1796, 2008
- 2 Curr. Med. Chem. 16: 4481-4489, 2009
- 3 Urol 81: 920.e1-5, 2013

Disclosures

Funding: University of Shizuoka **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Ethics Committees of the University of Shizuoka