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DIRECT EVIDENCE FOR SIGNIFICANT CONTRIBUTION OF IMIDAFENACIN EXCRETED IN THE URINE TO THE BLADDER-SELECTIVE PHARMACOLOGICAL EFFECTS

Hypothesis / aims of study

Imidafenacin, a potent and selective antagonist of M_1 and M_3-muscarinic receptor subtypes, is currently used for the treatment of overactive bladder [1,2]. Clinical studies have shown that this drug is safe, efficacious, and tolerable to control symptoms of overactive bladder even over the long term [4]. Pharmacological studies of this agent showed a significant selectivity of imidafenacin in the bladder over the salivary gland and brain [1]. We have shown that oral administration of imidafenacin at relatively low doses caused a more selective and longer-lasting binding to muscarinic receptors in the bladder of rats than at other tissues such as the salivary gland, heart, colon, lung and brain, suggesting preferential muscarinic receptor binding in the bladder [2]. Also, pharmacokinetic data revealed that the orally administered imidafenacin distributed at a higher concentration in the bladder than the serum or submaxillary gland [2]. The relatively high concentration of unchanged imidafenacin was shown to be excreted into the urine of humans receiving clinical dose of this agent, suggesting the contribution of urinary imidafenacin to the bladder pharmacological effect. Thus, the present study was undertaken to characterize in vivo muscarinic receptor binding of [^{3}H]imidafenacin (with high specific activity) in the bladder and other tissues of mice after the intravenous injection of the radioligand and also to examine directly the contribution of urinary [^{3}H]imidafenacin to the bladder receptor binding.

Study design, materials and methods

[^{3}H]imidafenacin (851 GBq/mmol, 12 nmol/kg) was injected in to the tail vein of mice. The mice were sacrificed under anesthesia with isoflran at 10, 30, 90 and 180 min. A blood sample was taken from the descending aorta and tissues (bladder, submaxillary gland, heart, colon, lung and cerebral cortex) were rapidly removed. Each tissue was homogenized in the ice-cold 50 mM Na^+/K^+ phosphate buffer. The particulate-bound radioactivity was determined by rapid filtration of 0.5 mL of tissue homogenates over Whatman CF/C filters, which were washed subsequently with 1 mL of ice-cold buffer. Radioactivity was measured in a liquid scintillation counter. The in vivo specific binding of [^{3}H]imidafenacin was estimated from the difference of particulate-bound radioactivity between vehicle and atropine (5 mg/kg i.p.)-pretreated mice, reflecting total binding and nonspecific binding of the radioligand, respectively. The specific [^{3}H]imidafenacin binding in tissues was also measured by the intravenous injection of the radioligand in mice received the bilateral ligation of ureters.

Results

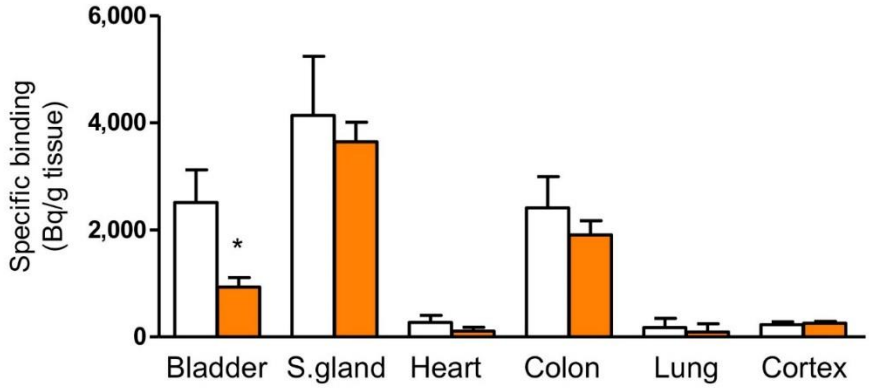
In the in vitro experiment, [^{3}H]imidafenacin was shown as a selective radioligand to bind specifically muscarinic receptors in the bladder and other tissues with high affinity. Following the intravenous injection of this radioligand, there was a significant amount of specific [^{3}H]imidafenacin binding in particulate fractions of the bladder, submaxillary gland, heart, lung and colon of mice, but not cerebral cortex. In the time course experiment, specific [^{3}H]imidafenacin binding in the bladder attained peak levels at 10 min after the injection and the degree of binding was sustained until 90 min, with considerable binding remaining even at 180 min. On the other hand, specific [^{3}H]imidafenacin binding in the submaxillary gland, heart, lung and colon was largest at 10 min, and it declined rapidly with the disappearance of [^{3}H]imidafenacin from the plasma. Notably, following the bilateral ligation of ureters compared with sham, there was a marked (63%) reduction of specific [^{3}H]imidafenacin binding in the bladder of mice received intravenous injection of the radioligand(Fig. 1).

Interpretation of results

These data demonstrated that imidafenacin distributed to the bladder wall from not only the blood but also the urine collected in the bladder.

Concluding message

The present study provides a direct in vivo evidence to demonstrate that imidafenacin exerts more selective and longer-lasting binding of muscarinic receptors in the bladder than other tissues and that such bladder selectivity is attributed significantly to the urinary imidafenacin excreted.



Each column represents mean±S.E. of 5-9 mice. *P<0.05 vs sham (Student's t-test).

Fig. 1 Specific [^{3}H]Imidafenacin binding in tissues after the intravenous injection of the ligand, in mice received bilateral ligation of ureters. Open bars are sham rats and filled bars are ureters ligating rats.

References
1. Arzneimittel-Forschung, 57: 147-154 (2007)
2. J Pharmacol Exp Ther, 336: 365-371 (2011)
3. Patient Prefer Adherence, 7: 111-120 (2013)

Disclosures
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