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Title: MUSCARINIC RECEPTOR BINDING CHARACTERISTICS OF A NOVEL ANTICHOLINERGIC AGENT, YM-905, IN THE URINARY BLADDER AND OTHER TISSUES OF MICE

Aims of Study.

Antimuscarinic agents such as oxybutynin are widely used for the treatment of detrusor instability (DI) or detrusor hyperreflexia which is characterized by symptoms of increased frequency of micturition and urge urinary incontinence [1]. However, the use of this drug is often limited by systemic side effects such as dry mouth. Thus, the bladder-selective anticholinergic agents receive a great deal of attention, in terms of the development of effective therapeutic agents with less side effects. YM-905 ((+)-(1S,3'R)-quinuclidin-3'-yl-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate), an antimuscarinic agent that is being developed for therapeutic use in the treatment of overactive bladder with symptoms of frequency, urgency and urge urinary incontinence. The therapeutic effect and dry mouth by anticholinergic agents in patients with DI are mainly based on the blockade of muscarinic receptors in the urinary bladder and salivary gland, respectively. Currently, our studies have highlighted the usefulness of *in vivo* analysis of drug-receptor binding in relation to the pharmacokinetics for characterizing pharmacological specificity (potency, duration of action and tissue selectivity) of the drug [2-4]. To clarify the *in vivo* blockade by YM-905 of muscarinic receptors, we measured the specific binding of [N-methyl-^{3}H]scopolamine (NMS) in various tissues of mice including the urinary bladder, after oral administration of this agent, compared with that of oxybutynin.

Methods.

At 0.5 to 24 hr after the oral administration of YM-905 or oxybutynin, mice were sacrificed by exsanguination from the descending aorta, and the bladder, prostate, submaxillary gland, heart, colon and lung were dissected. The mucarinic receptor in each tissue was measured by a radioreceptor binding assay with [^{3}H]NMS as a radioligand, and binding constants of apparent dissociation constant (K_d) and maximal number of binding sites (B_{max}) for [^{3}H]NMS were estimated by Scatchard analysis. The *in vitro* inhibitory effects by YM-905 and oxybutynin of specific [^{3}H]NMS binding in mouse tissues were also examined. The concentration of YM-905 in the plasma was also measured.

Results.

YM-905 (3-1000 nM) reduced specific [^{3}H]NMS binding in the bladder, submaxillary gland and heart in a concentration-dependent manner. The order of inhibitory effect by this agent was the submaxillary galnd>bladder>heart. Similar inhibitory potency of specific [^{3}H]NMS binding in each tissue was seen by oxybutynin. Following the oral administration of YM-905 (20.8, 62.4, 208 mol/kg), there was a dose-dependent and significant increase in K_d values for specific [^{3}H]NMS binding in the bladder, prostate, submaxillary gland, heart, colon and lung of mice compared with each control valule, with no or slight change of B_{max} values. Such increase in K_d value in each tissue attained to the maximal level 2 hr after the oral administration of YM-905, and maintained up to 6 and/or 12 hr. In contrast, the plasma concentration of YM-905 was maximal at 0.5 hr after the oral administration and then reduced with time.

The oral administration of oxybutynin at the dose of 76.1 mol/kg brought about a significant increase in K_d

value for specific [^{3}H]NMS binding in the bladder, prostate, submaxillary gland, heart, colon and lung of mice, and there was little reduction of B_{max} value in each tissue. The increment of K_d value by the oxybutynin administration was maximal at 0.5 hr later, markedly reduced at 2 hr later, and disappeared at 6 hr.

Conclusions.

These data indicate that YM-905 binds competitively to the muscarinic receptors in the mouse urinary bladder, and that, compared with that of oxybutynin, the muscarinic receptor blockade after the oral administration of YM-905 may develop more slowly and it may be of a longer duration. Thus, it is speculated that such slow kinetics of muscarinic receptor binding by the orally administered YM-905 may contribute to the slow onset and prolonged duration of pharmacological effects with less incidence of side effects. These findings support the usefulness of YM-905 as a therapeutic agent for overactive bladder with symptoms of frequency, urgency and urge urinary incontinence.

References.

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