

MUSCARINIC RECEPTOR BINDING CHARACTERISTICS OF ANTICHOLINERGIC AGENTS TO TREAT OVERACTIVE BLADDER, IN HUMAN BLADDER AND PAROTID GLAND

Hypothesis / aims of study

Anticholinergic agents such as oxybutynin (Oxy) are widely used for the treatment of overactive bladder (OAB) with symptoms of frequency, urgency and urge incontinence. However, its use is often limited by the systemic side effects such as dry mouth, which occur frequently as serious problems in patients receiving this treatment [1]. The therapeutic effect and dry mouth by anticholinergic agents in patients with OAB are mainly based on the blockade of muscarinic receptors (mAChRs) in the urinary bladder and salivary gland, respectively. Thus, the bladder-selective anticholinergic agents receive a great deal of attention, in terms of the development of effective therapeutic agents with less side effect. Propiverine (Prop) [2] and tolterodine (Tol) [3] are considered as relatively bladder-selective anticholinergic agents for the treatment of OAB with less incidence of dry mouth than Oxy. To clarify the bladder selectivity of anticholinergic agents to treat OAB, in human bladder and parotid gland, we examined mAChR binding affinities of Oxy, Prop, Tol, their active metabolites (N-desethyl-oxybutynin: DEOB, 1-methyl-4-piperidyl benzilate N-oxide: DPr-P-4(N→O), 5-hydroxymethyl metabolite: 5-HM, respectively) and darifenacin (Darife).

Study design, materials and methods

Specimens of human urinary bladder were obtained from patients who underwent total cystectomy due to bladder tumor. Specimens of human parotid gland were obtained from patients with the surgical excision of parotid tumor. The tissue preparations were taken from the intact part of each specimen. The mAChRs in homogenates of human bladder and parotid gland were measured by a radioreceptor binding assay with [N-methyl-³H]scopolamine (NMS) as a radioligand, and binding parameters of apparent dissociation constant (K_d) and maximal number of binding sites (B_{max}) for [³H]NMS were estimated by Scatchard analysis. The inhibitory effects of anticholinergic agents on specific [³H]NMS binding in the bladder and parotid gland were examined and their inhibition constants (K_i) were estimated.

Results

Specific binding of [³H]NMS in the human bladder and parotid gland was saturable and of high affinity, which characterized a selective labeling of mAChRs. The K_d value in the human parotid gland compared with the bladder was significantly lower and B_{max} value was larger. Oxy, Prop, Tol, their metabolites and Darife inhibited competitively specific [³H]NMS binding in both tissues in a concentration-dependent manner. Based on the K_i values, the inhibitory effects of Tol, 5-HM and DPr-P-4(N→O) were greater in the bladder than in the parotid gland, whereas the inhibitory effects of Oxy, DEOB, Prop and Darife were greater in the parotid gland.

Interpretation of results

Based on the ratios of K_i values in the bladder over parotid gland, Tol, 5-HM and DPr-P-4(N→O) exhibited 3-4 times greater affinity to the human bladder mAChRs than Oxy.

Concluding message

It is concluded that Tol, 5-HM and DPr-P-4(N→O) bind more selectively to mAChRs in the human bladder than in the parotid gland. Thus, the present study may provide a rationale for the pharmacological usefulness of Tol and Prop as therapeutic agents of OAB.

References

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