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IN VITRO TISSUE SELECTIVE PROFILE OF SOLIFENACIN SUCCINATE (YM905) FOR URINARY BLADDER OVER SALIVARY GRAND IN RATS AND MONKEYS

Aims of Study

Antimuscarinic agents are currently used for the treatment of urge incontinence and other symptoms of overactive bladder (OAB). However, the use of these agents is often limited by severe adverse effects, particularly dry mouth. In the present study, we investigated the tissue selectivity of solifenacin succinate (YM905), a novel muscarinic receptor antagonist being developed for the treatment of OAB, for urinary bladder over salivary gland in rats and monkeys. The results were compared with those of other antimuscarinics such as tolterodine, oxybutynin and darifenacin in vitro.

Methods

Bladders and submandibular glands were isolated from rats and monkeys, and dispersed single cells were yielded by enzymatic digestion of the tissues. The cells of each tissue were loaded with fluorochrome Fura 2. Carbachol (CCh)-induced intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) elevation were then monitored as a ratio of fluorescence intensities (500 nm) excited at wavelengths of 340 and 380 nm using a spectrofluorometer. In each cell preparation, the concentration-response relation for CCh was confirmed. Antimuscarinics were added and incubated for 2-min before application of CCh (10 μM). Inhibitory potency was estimated as an affinity constant (pKi value) for each antimuscarinic agent, and the bladder selectivity ratio (R) was calculated by the following equation: R = [Ki (submandibular gland)] / [Ki (urinary bladder)].

Results

In rat tissue cells, solifenacin inhibited CCh-induced $[Ca^{2+}]i$ elevation in a concentration-dependent manner. The inhibitory potency of solifenacin in bladder smooth muscle cells (pKi = 8.12) was significantly greater than that in submandibular gland cells (pKi = 7.57). Although the inhibitory potencies of other antimuscarinics in bladder smooth muscle cells were significantly greater than those in submandibular gland cells, the bladder selectivity of solifenacin (R = 3.6) was greater than that of tolterodine (R = 2.0), oxybutynin (R = 2.1) or darifenacin (R = 1.7). The inhibitory effect of solifenacin in monkey bladder smooth muscle cells (pKi = 8.52) was equivalent to those of other antimuscarinics, although it was weaker for inhibiting submandibular gland cells (pKi = 8.21) (Table 1). Only solifenacin showed bladder selectivity (R = 2.1), which was significantly greater than other antimuscarinics (R = 0.46 - 0.65).

Table 1. Inhibitory effects of solifenacin and other antimuscarinics on CCh-induced $[Ca^{2+}]i$ elevation in bladder smooth muscle cells and submandibular gland cells isolated from monkeys

Antimuscarinics	pKi value		Bladder selectivity ratio (R)
	Bladder smooth muscle cells	Submandibular gland cells	
Solifenacin	8.52 ± 0.05	8.21 ± 0.05	2.1 ± 0.38 ##
Tolterodine	8.50 ± 0.04	8.70 ± 0.04	0.65 ± 0.06
Oxybutynin	8.68 ± 0.06	8.99 ± 0.01	0.51 ± 0.08
Darifenacin	8.39 ± 0.07	8.75 ± 0.06	0.46 ± 0.06

Each value represents mean ± S.E.M. of 5 monkeys.

[##] Statistically different from tolterodine, oxybutynin and darifenacin ($P<0.01$; two-way Tukey′s test).

Conclusions

Solifenacin displays tissue selectivity towards urinary bladders over salivary gland in both rats and monkeys. The bladder selective profile of solifenacin may contribute to a beneficial separation between desired bladder effects and adverse effects, such as dry mouth, in humans.