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Muscarinic receptors in the bladder: from basic research to therapeutics

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Muscarinic receptor antagonists (antimuscarinics) serve as the cornerstone in the pharmacological management of overactive bladder (OAB) by relieving the symptoms of urgency, frequency and incontinence. These drugs operate primarily by antagonizing post-junctional excitatory muscarinic receptors (M_2/M_3) in the detrusor. The combination of pharmacological and gene knockout studies has greatly advanced our understanding of the functional role of muscarinic receptors in the bladder. M_3 receptors produce direct smooth muscle contraction by a mechanism that relies on entry of extracellular calcium through L-type channels and activation of a rho kinase. M_2 receptors, which predominate in number, appear to facilitate M_3-mediated contractions. M_2 receptors can also produce bladder contractions indirectly by reversing cAMP-dependent β-adrenoceptor-mediated relaxation, although the physiological role of β-adrenoceptors in detrusor relaxation is controversial. Emerging evidence suggests that muscarinic receptors in the urothelium/suburothelium can modulate the release of certain factors, which in turn may affect bladder function at the efferent or afferent axis. Currently, oxybutynin, tolterodine, darifenacin, solifenacin and trospium are the five major antimuscarinics approved for the treatment of OAB. Comparative clinical studies have shown that oxybutynin and solifenacin may be marginally more effective than tolterodine, although the latter seems to be better tolerated. Pharmacokinetic–pharmacodynamic analyses using plasma concentrations of 'total drug' indicate that, at therapeutic doses, the clinical efficacy of darifenacin and solifenacin may be driven primarily by selective M_3 receptor occupation, whereas the pharmacodynamic effects of pan-selective molecules (such as tolterodine, trospium) may potentially involve multiple receptors, including M_2 and M_3. Furthermore, high M_3 receptor occupation is the likely explanation for the greater propensity of darifenacin and oxybutynin to cause dry mouth and/or constipation. Although the recently introduced drugs represent a significant improvement over older drugs, especially with respect to the convenience of dosing schedule, their overall efficacy and tolerability profile is still less than optimal and patient persistence with therapy is low. Recent advances in basic research have not yet offered a clear discovery path for improving the therapeutic index of antimuscarinic molecules. There is still an unmet need for an antimuscarinic medicine with superior clinical effectiveness that can translate into better persistence on therapy.
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Keywords: Muscarinic; antimuscarinic; tolterodine; oxybutynin; darifenacin; solifenacin; trospium; overactive bladder; micturition

Abbreviations: AC, adenylyl cyclase; ACh, acetylcholine; CaM, calmodulin; cAMP, cyclic 3′,5′-adenosine monophosphate; 4-DAMP, 4-diphenylacetoxy-*N*-methylpiperidine methobromide; ER, extended release; IR, immediate release; KO, knockout; MLCP, myosin light chain phosphatase; OAB, overactive bladder; *p*-F-HHSid, *p*-fluorohexahydrosiladifenidol; PK–PD, pharmacokinetics–pharmacodynamics; TDS, transdermal

Introduction

Overactive bladder (OAB) is a highly prevalent disorder characterized as a syndrome consisting of 'urgency with or without urgency incontinence, usually accompanied by frequency and nocturia' (see Wein & Rovner, 2002; Abrams *et al*., 2003). The process of micturition is critically dependent on the operation of a spinal–bulbospinal reflex, which comprises afferent (sensory) and efferent (motor) pathways that are integrated and coordinated at spinal and supraspinal centers (see de Groat *et al*., 1993). The lumbosacral parasympathetic outflow provides the excitatory motor input to the urinary bladder smooth muscle (detrusor). It is generally accepted that activation of muscarinic receptors on the detrusor is one of the mechanisms driving abnormal detrusor overactivity in the diseased bladder (see de Groat, 1997). Recent evidence, however, has raised the possibility of a potential role of urothelial/suburothelial muscarinic receptors in the etiology of detrusor overactivity or sensory urgency (see Andersson & Yoshida, 2003; de Groat, 2004). Regardless of the precise locus of action of antimuscarinic drugs (i.e., afferent or efferent), their widespread use for the treatment of OAB over the past three decades underscores the critical role of muscarinic receptors in the pathophysiology of this disorder. Recent advances in our understanding of muscarinic receptor pharmacology in the lower urinary tract have guided the discovery and development of new medicines for OAB (see Chapple *et al*., 2002; Chess-Williams *et al*., 2001; Hegde *et al*.,

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2004). The objective of this review is to summarize our current understanding of the functional role of muscarinic receptor subtypes in the bladder and to analyze the clinical and pharmacokinetic–pharmacodynamic (PK–PD) profile of marketed antimuscarinic drugs.

Muscarinic receptor pharmacology of the bladder

Pharmacological studies

Muscarinic receptors are classified, based on molecular and pharmacological criteria, into five subtypes (M_1–M_5) (see Caulfield & Birdsall, 1998). Radioligand saturation and competition-binding studies have shown that the bladder of most species, including man, is endowed principally with M_2 and M_3 receptors, with the former predominating in number (see Hegde & Eglen, 1999). It is pertinent to note that these studies are not sensitive enough to detect the muscarinic receptor population in nondetrusor components (e.g., nerves, urothelium) of the bladder, which make up a small fraction of the total tissue mass but nevertheless may be important from a functional standpoint.

Until recently, our understanding of the relative contribution of muscarinic receptor subtypes towards bladder function was derived primarily from pharmacological studies using molecules such as pirenzepine, 4-DAMP, *p*-F-HHSid, darifenacin and methoctramine, which have preferential affinity for one or more subtypes. These studies have suggested that the M_3 receptor primarily mediates direct contractile responses to agonists in the normal bladder (Wang *et al*., 1995; Hegde *et al*., 1997; Chess-Williams *et al*., 2001; Fetscher *et al*., 2002). It was originally thought that the M_3 contractile response in the bladder is mediated by intracellular calcium that is mobilized by inositol phosphates that are generated following activation of phospholipase C (Harriss *et al*., 1995). This assumption has been re-examined by a recent study that concluded, based on the inhibitory effects of a range of molecules that selectively target different transductional pathways, that M_3-mediated contraction of the human bladder depends on entry of extracellular calcium through L-type calcium channels and activation of a rho kinase (Schneider *et al*., 2004). Pharmacological results have failed to demonstrate a role of M_2 muscarinic receptors in mediating direct contractile responses, suggesting that this receptor either plays little or no role, or that the presence of the M_3 receptor is obligatory for its functional role (see the discussion below on findings from gene knockout (KO) studies). It has been suggested that the relative contribution of M_2 receptors toward the overall direct contractile response becomes more important in diseased states (Pontari *et al*., 2004), although this finding has recently been challenged (Stevens *et al*., 2004a, b).

A key functional role of the dominant M_2 receptors appears to be in mediating an indirect contractile response by reversing β-adrenoceptor-mediated relaxation through a cAMP-dependent mechanism (Hegde *et al*., 1997; Yamanishi *et al*., 2000). This effect can be demonstrated by first inactivating the M_3 receptor with a nitrogen mustard derivate of 4-DAMP and then measuring the contractile response to the muscarinic agonist in the presence of heterologous contractile (KCl) and relaxant (isoprenaline) agents. It should be noted, however, that the physiological role of the sympathetic nervous system and β-adrenoceptors in bladder relaxation is controversial (Andersson, 1999) and there are no studies that have attempted to study the indirect role of M_2 receptors in the human bladder.

Parasympathetic nerves innervating the bladder are enriched with pre-junctional inhibitory and facilitatory muscarinic receptors that are differentially activated, depending on the frequency of nerve stimulation. Using pharmacological tools, the prejunctional faciliatory receptor has been classified as M_1 (Somogyi *et al*., 1994; Tobin & Sjogren, 1995), whereas the prejunctional inhibitory receptor has been classified as either M_2 (Tobin & Sjogren, 1995) or M_4 (D'Agostino *et al*., 2000).

The urothelium was traditionally viewed as a passive membrane barrier between the urinary tract and its contents. However, emerging evidence suggests that the urothelium and suburothelial interstitial cells, which express a range of receptors, including muscarinic (Gillespie *et al*., 2003), actively participate in sensory function in the bladder by releasing neurotransmitters in response to distention and receptor activation (de Groat, 2004). Muscarinic receptors on the urothelial lining of the bladder have been shown to evoke the release of a diffusible mediator that inhibits contraction of the underlying detrusor muscle (Fovaeus *et al*., 1999; Hawthorn *et al*., 2000). Upon activation of muscarinic receptors, urothelial cells have been shown to release ATP, which in turn may activate afferent nerves to alter its excitability (see de Groat, 2004). The source of acetylcholine (ACh) (neuronal/extraneuronal) mediating the urothelial responses and its role in the pathophysiology of OAB remains to be elucidated and is the subject of extensive ongoing basic research.

Gene KO studies

In recent years, mutant mice deficient in one or more muscarinic receptor subtype have been constructed and used to assess the contribution of the five subtypes in bladder function. The findings from these gene KO studies have essentially confirmed the conclusions derived from pharmacological studies and also added new insights to our understanding of the role of muscarinic receptors in the physiology of the lower urinary tract.

In M_3 KO mice, bladder contractile responses to carbachol are attenuated by $\sim$95%, consistent with findings from pharmacological studies that have ascribed a major role of M_3 receptors in mediating direct contraction of the bladder (Matsui *et al*., 2002; Ehlert *et al*., 2005). Interestingly, cystometric studies have shown that, although M_3 KO animals have longer voiding intervals and larger micturition volumes and bladder capacity than wild-type controls, the bladder residual volume in these animals is unchanged, indicating no major functional impairment of bladder emptying (Igawa *et al*., 2004). A possible explanation for this finding is that chronic absence of the M_3 receptor is compensated by either another muscarinic receptor or noncholinergic mechanisms.

The residual ($\sim$5%) direct contractile responses that persist in M_3 KO mice are completely lost in mice lacking both M_2 and M_3 receptors, implying that the M_2 receptor is capable of mediating small direct contractile responses (Matsui *et al*., 2002). Interestingly, the contractile responses to oxotremorine-M were more greatly inhibited by 4-DAMP mustard (M_3 inactivation) in the bladder tissue of M_2 KO than in wild-type

mice, implying that M_2 receptors can also operate by enhancing M_3-mediated contractions and this effect is manifested only in wild-type mice (Ehlert *et al*., 2005). Cystometric studies have demonstrated small increases in voiding intervals and micturition volumes in M_2 KO animals (Igawa *et al*., 2004). Given the potential interaction between M_2 and M_3 receptors, it seems relevant to conduct cystometric studies in animals lacking M_2 and M_3 receptors, particularly as atropine's effects on cystometric parameters are more marked than that observed in M_3 or M_2 KO animals (Igawa *et al*., 2004). The biochemical mechanisms underlying the potential crosstalk between M_2 and M_3 receptors are unclear at present. The indirect c-AMP-related contractile effects of M_2 receptor activation have also been confirmed using M_2 and M_3 KO animals (Matsui *et al*., 2003; Ehlert *et al*., 2005). In bladders from M_3 KO mice that were precontracted with PGF2alpha and relaxed with isoprenaline or forskolin, oxotremorine produced concentration-dependent contractile responses that exhibited an M_2 profile in competitive antagonism studies and were completely abolished in M_2/M_3 KO mice.

As stated previously, pharmacological studies have been unable to discern whether the prejunctional inhibitory autoreceptors in the bladder belong to the M_2 or M_4 subtypes, owing to the paucity of molecules that discriminate between M_2 and M_4 receptors. This ambiguity has been clarified by use of M_2 and M_4 KO animals. In electrically stimulated bladder segments, pre-incubated with [^{3}H]choline and superfused with oxotremorine, ipratropium stimulated tritium outflow in wild-type and M_2 KO bladders, but had no effect in M_4 KO bladders (Zhou *et al*., 2002). These studies clearly implicate a key role of M_4 receptors in regulating *ACh* release from post-ganglionic cholinergic nerves *via* a negative feedback mechanism. The existence of facilitatory M_1 receptors, whose presence has been demonstrated pharmacologically, has yet to be confirmed by gene KO studies.

Figure 1 summarizes our current understanding of the pharmacological role of muscarinic receptor subtypes in control of bladder function. The collective evidence from pharmacological and gene KO studies have added immense confidence to our knowledge base and may potentially guide the discovery of novel medicines for the treatment of OAB.

Implications for drug discovery

A muscarinic antagonist used for the treatment of OAB should ideally normalize bladder function without causing secondary antimuscarinic adverse effects, chiefly dry mouth. Given the critical role of M_3 receptors in mediating direct bladder contraction, antagonism of this receptor would be expected to result in some level of efficacy in OAB patients. Unfortunately,

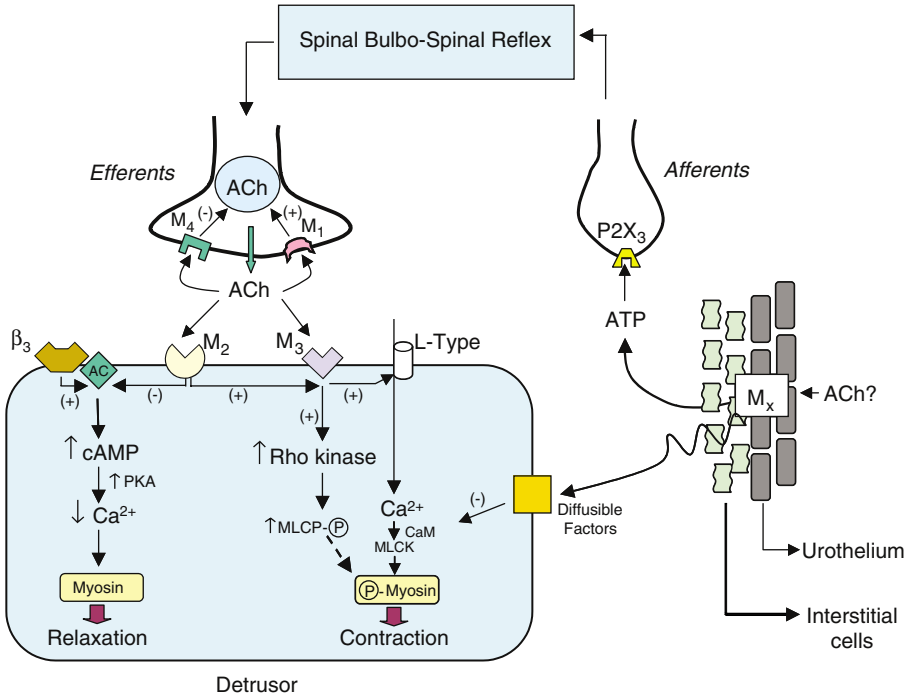

Figure 1 Schematic showing the role of muscarinic receptor subtypes in modulation of detrusor contractility. The micturition reflex is dependent on the operation of the spinal–bulbospinal reflex. Detrusor contractile tone is dependent on the phosphorylation state of myosin filaments. The lumbosacral parasympathetic outflow provides the major excitatory efferent input to the detrusor. *ACh* release from post-ganglionic parasympathetic nerves is regulated by prejunctional inhibitory M_4 and facilitatory M_1 receptors. ACh agonizes detrusor M_3 receptors to produce 'direct contraction' by a mechanism that relies on entry of extracellular calcium (Ca^{2+}) through L-type calcium channels. Interaction of Ca^{2+} with calmodulin (CaM) activates myosin light chain kinase (MLCK), resulting in contraction. M_3 receptor activation can also activate a rho kinase that inactivates myosin light chain phosphatase (MLCP) and promotes detrusor contraction. M_2 receptors can modulate M_3-mediated 'direct contractions' by a mechanism that is not clearly understood. Activation of M_2 receptors by *ACh* inhibits AC to produce 'indirect contractions' by inhibiting cAMP-dependent β-adrenoceptor mediated relaxation. *ACh*, from neuronal or non-neuronal sources, can potentially activate muscarinic receptors (Mx, subtype unknown) on urothelial/sub-urothelial cells to release ATP, which in turn can alter excitability of afferent nerves *via* $P2X_3$ receptors. Activation of muscarinic receptors (Mx, subtype unknown) can also evoke the release of diffusible factors from urothelial/sub-urothelial cells to modulate detrusor contractility indirectly.

both pharmacological and gene KO studies have shown that M_3 receptors mediate, at least in part, the sialogogue response to muscarinic agonists (Nakamura *et al*., 2004). This paradigm poses considerable challenges to the discovery of an efficacious muscarinic antagonist that is devoid of dry mouth. Given the potential crosstalk between M_2 and M_3 receptors and the important indirect role of M_2 receptors in mediating bladder contraction, the strategy of selectively targeting the M_2 receptor for OAB has some merit, but is clinically unprecedented and carries the risk of cardiac adverse effects.

Comparative analysis of approved antimuscarinic drugs

Pharmacological profile

Currently, oxybutynin, tolterodine, solifenacin, darifenacin and trospium are the five major antimuscarinic drugs that are employed for the treatment of OAB. These molecules differ in their pharmacological profile at the five human recombinant muscarinic receptors (Table 1). Tolterodine (including its 5-hydroxymethyl metabolite) and trospium essentially do not discriminate between the five subtypes. Oxybutynin (and its *N*-desethyl metabolite) and solifenacin do possess marginal selectivity ($\sim$ 10-fold) for M_3 over the M_2/M_5 subtypes, but do not distinguish between M_3 and M_1/M_4 subtypes. In contrast, darifenacin, which behaves as an insurmountable antagonist (Fetscher *et al*., 2002), has a high degree of selectivity for M_3 over the M_2/M_4 subtypes and modest selectivity for M_3 over the M_1/M_5 subtypes. In animal models, greater bladder-to-salivary gland selectivity ratios have been reported for tolterodine ((Nilvebrant *et al*., 1997a; Gillberg *et al*., 1998), darifenacin (Gupta *et al*., 2002) and solifenacin (Ikeda *et al*., 2002) compared to oxybutynin.

Clinical efficacy and adverse effect profile

The effectiveness of antimuscarinic drugs in OAB has been well established with a number of molecules, but the magnitude of efficacy is modest and its clinical significance has been questioned (see Herbison *et al*. (2003) for review). Data from large controlled trials have been published for most of the marketed antimuscarnic drugs, including the five commonly used oral products (tolterodine-ER, oxybutynin-ER, solifenacin, darifenacin and trospium) and one transdermal product (oxybutynin-TDS) (see Chapple *et al*. (2005c) for a systematic review and meta-analysis of all trials). The data from the vast majority of these studies cannot, however, be used to make relative comparisons of efficacy and tolerability, given the inconsistent placebo response and lack of standardization of enrollment criteria and measurement instruments. Taking this caveat into consideration, it is worth noting, however, that the efficacy of these drugs falls within a narrow range with respect to reduction in incontinence episode frequency (-43 to -77%) or voiding frequency (-16 to -28%) (Table 2). Likewise, with the exception of oxybutynin-TDS, the incidence of dry mouth for these molecules is roughly in the range of 22–35% (Table 2). Although dry mouth is not an issue with oxybutynin-TDS, pruritis at the application site is a limitation of this product. Compared to the other drugs, darifenacin does appear to produce a higher incidence of constipation, especially at the higher dose.

Head-to-head comparative studies have been conducted in a few instances and offer the opportunity of making a cogent scientific assessment of relative efficacy and tolerability. Two such trials have been published thus far using tolterodine ER as the common comparator drug. In the first case (OPERA Trial), the efficacy and tolerability of tolterodine-ER (4 mg, qd) was compared to oxybutynin-ER (10 mg, qd) in a randomized, double-blind, 12-week study in 790 women (Diokno *et al*., 2003). Both medications produced similar reductions in the weekly frequency of urge urinary incontinence (primary end point) and total incontinence episodes. However, the percent reduction in weekly micturition frequency was significantly greater and the percent of patients reporting complete control of continence was statistically higher in the oxybutynin-ER group compared to the tolterodine-ER group. Dry mouth was reported by a greater number of patients on oxybutynin-ER (30%) than on tolterodine ER (22%). In the second case (STAR Trial), solifenacin (flexible dosing, 5 or 10 mg, qd) was compared to tolterodine ER (4 mg, qd) in a double-blind, double-dummy, 12-week study in 1355 patients (Chapple *et al*., 2005b). Solifenacin produced statistically significantly greater reductions in episodes of urgency, urge incontinence and overall incontinence compared to tolterodine-ER. More solifenacin-treated patients became continent and reported improvements in perception of their bladder condition. Adverse effect profiles of the two drugs were roughly comparable.

PK–PD

A major attribute of recently introduced antimuscarinic drugs is their convenient dosing flexibility. With the exception of trospium, which is dosed twice daily, the remaining four oral

Table 1 Affinity of antimuscarinics for human muscarinic receptor subtypes

Molecule	M_1	M_2	M_3	M_4	M_5	*References*
Oxybutynin	1.0	6.7	0.67	2.0	11.0	Nilvebrant *et al*. (1997a); Gillberg *et al*. (1998)
Tolterodine	3.0	3.8	3.4	5.0	3.4	Nilvebrant *et al*. (1997a); Gillberg *et al*. (1998)
Darifenacin	7.3	46.0	0.79	46.0	9.6	Nilvebrant *et al*. (1997a); Gillberg *et al*. (1998)
Solifenacin	25	125	10	NR	NR	Ikeda *et al*. (2002)
Trospium	0.75	0.65	0.50	1.0	2.3	Napier & Gupta (2002)

All values represent binding affinity estimates (K_i, nM) at human recombinant muscarinic receptors. The pharmacology of the active metabolites of tolterodine (5-hydroxymethyl metabolite) and oxybutynin (*N*-desthyl oxybutynin) is similar to that of the corresponding parent molecules (Nilvebrant *et al*., 1997b; Waldeck *et al*., 1997).
NR: not reported.

Table 2 Clinical efficacy and adverse effects of marketed antimuscarinics for OAB (12-week trials)

Dose	*Tolterodine-ER 4 mg, qd*	*Oxybutynin-ER 10 mg, qd*	*Oxybutynin-TDS 3.9 mg day^{-1}*	*Solifenacin 5 mg, qd*	*Solifenacin 10 mg, qd*	*Darifenacin 7.5 mg, qd*	*Darifenacin 15 mg, qd*	*Trospium 20 mg, bid*
Incontinence episodes (% change from baseline)	−53, −69, −43	−72	−61	−61	−52	−68	−77	−59
Micturition frequency (% change from baseline)	−16, −25, −19	−28	−19	−20	−22	−17	−17	−19
Dry mouth (%)	23, 22, 24	30	4	8	23	20	35	22
Constipation (%)	6, 8, 3	6	—	4	9	15	21	9
Pruritis (%)	—	—	14	—	—	—	—	—
References	Van Kerrebroeck *et al.* (2001); Diokno *et al.* (2003); Chapple *et al.* (2005b)	Diokno *et al.* (2003)	Dmochowski *et al.* (2003)	Cardozo *et al.* (2004)	Cardozo *et al.* (2004)	Chapple *et al.* (2005a)	Chapple *et al.* (2005a)	Zinner *et al.* (2004)

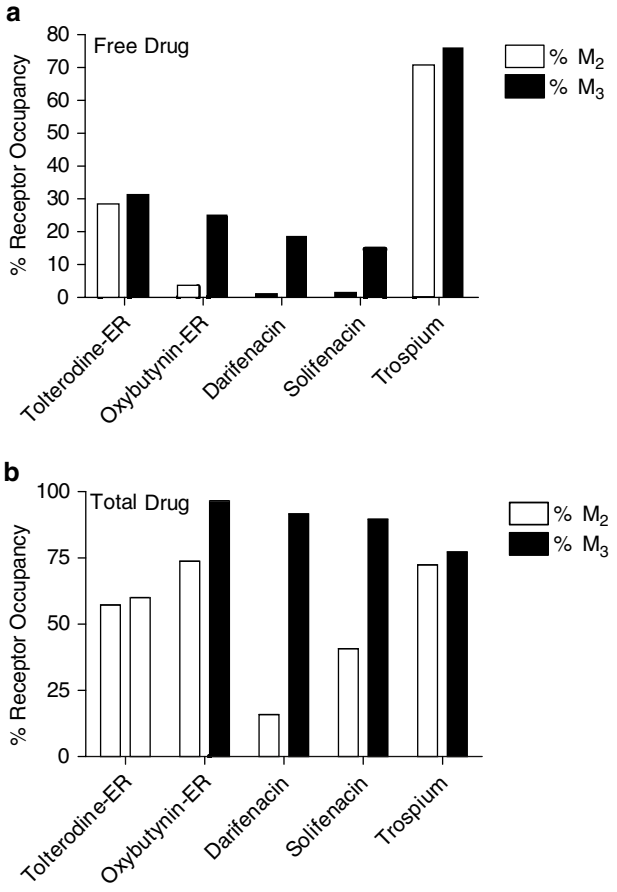

Figure 2 Estimated M_2 and M_3 receptor occupancy at free (a) and total (b) plasma drug levels of antimuscarinic drugs. Hill–Langmuir equation was used to compute receptor occupancy by using binding affinity constants of the drugs at the human M_2 and M_3 recombinant receptors (Table 1) and average plasma drug levels (C_{avg}, total drug) achieved in humans at therapeutic doses of tolterodine-ER (4 mg, qd), oxybutynin-ER (10 mg, qd), darifenacin (15 mg, qd), solifenacin (10 mg, qd) and trospium (20 mg, bid) (Table 3). In the case of oxybutynin and tolterodine, the contributions of both parent and active metabolite were taken into consideration to estimate the net receptor occupancy.

drugs (tolterdoine-ER, oxybutynin-ER, solifenacin and darifenacin) are dosed once daily. Table 3 summarizes the human exposure (C_{max}, AUC, Cavg) of the five molecules at their therapeutic doses. The C_{avg} (free fraction and total drug) was used to estimate % M_2 and M_3 receptor occupancies at therapeutic doses (Figure 2). As shown in Figure 2a, the 'free fraction' receptor occupancy estimates appear to be unrealistically low for all drugs, with the exception of solifenacin. This could imply that the pharmacodynamic effects of some of the drugs are driven by the local detrusor concentrations, as opposed to plasma drug levels, possibly as a result of partitioning of molecules into tissues. An alternate explanation is that protein binding has a marginal effect on drug concentrations at the receptor compartment. It is pertinent to note that the affinity of most drugs for plasma protein-binding sites is usually in the low micromolar level. Consequently, for drugs which have nanomolar affinity for their therapeutic targets, protein binding would be expected to have a negligible effect on the drug–receptor equilibrium. If one reflects on the 'total drug' receptor occupancy estimates

Table 3 Steady-state exposure of oral antimuscarinics at therapeutic doses

Drug		C_{max} (ng ml^{-1})	*AUC* (ng ml^{-1} h)	C_{avg}[a] ng ml^{-1}(nM)		*Protein binding (%)*	*References*
				Total	*Free*		
Tolterdine-ER[b] 4 mg, qd	Tolterodine	1.9	16.9	0.70 (2.2)	0.03 (0.1)	96	Olsson & Szamosi (2001)
	5-HM Tol[c]	2.5	32.1	1.3 (2.9)	0.47 (1.4)	64	
Oxybutynin-ER 10 mg, qd	R-Oxybutynin	1.1	18	0.75 (2.1)	0.0075 (0.02)	99	Sathyan *et al.* (2001)
	R-DE Oxybutynin[d]	8.3	132	5.5 (16.8)	0.055 (0.2)	99	
Solifenacin 10 mg, qd		40.6	749	31.2 (86.2)	0.62 (1.7)	98	Smulders *et al.* (2004)
Darifenacin[b] 15 mg, qd		5.8	88.9	3.7 (8.7)	0.074 (0.2)	98	Kerbusch *et al.* (2003)
Trospium 20 mg, bid		2.3	17.7	0.73 (1.7)	0.67 (1.6)	~50	Doroshyenko *et al.* (2005)

[a]C_{avg} = AUC (0–24 h)/24.
[b]Data in extensive metabolizers.
[c]5-HM tolterodine: 5-hydroxymethyl tolterodine.
[d]R-DE oxybutynin: R-desethyl oxybutynin.

(Figure 2b), it is striking that the five molecules possess roughly similar clinical efficacy despite producing divergent occupancy of the M_3 receptor, the key target that has been implicated in modulation of bladder function. This suggests that the antimuscarinic mechanism by which the drugs produce their pharmacodynamic effects may be more complex than previously envisaged. For example, it is possible that the efficacies of darifenacin and solifenacin result solely from high and preferential M_3 receptor antagonism, whereas those of pan-selective molecules (tolterodine, trospium) result from antagonism of multiple receptors including M_2. This is not unreasonable to postulate, since inhibition of bladder function can theoretically result from antagonism of post-junctional M_2/M_3 receptors or prejunctional facilitatory M_1 receptors (Figure 1). There does appear to be, however, some relationship between the estimates of M_3 receptor occupancy and incidence of dry mouth. Both darifenacin and oxybutynin-ER, which produce 92–96% M_3 receptor occupancy, tend to produce a higher incidence of dry mouth when compared to tolterodine, which occupies approximately 65% of M_3 receptors at therapeutic doses. The selective occupation of the M_3 receptor in the gastrointestinal tract by darifenacin may also be the mechanism for its greater propensity to cause constipation, but it is unclear as why solfenacin does not share this property.

Compliance and persistence on antimuscarinic drugs

Given the chronic nature of OAB, long-term compliance and persistence on antimuscarinic drugs is essential for engendering meaningful improvements in patient's quality of life, reduction in comorbidities and lowering of healthcare costs (see Noe *et al.*, 2004; Haab & Castro-Diaz, 2005). The convenience of once-daily dosing with newer antimuscarinic medicines has led to expected improvements in patient's compliance on therapy. The likelihood of patients to persist on a given therapy for a protracted period (>1 year), however, is dependent on their own assessment of the medicine's overall effectiveness and tolerability. In long-term, open-label studies, the percentage of patients who persist on therapy for the duration of the study (approximately 10–12 months) was 46, 76, 81 and 81% for oxybutynin-ER (Diokno *et al.*, 2002), tolterodine-ER (Kreder *et al.*, 2002), trospium (Halaska *et al.*, 2003) and solifenacin (Haab *et al.*, 2005), respectively. It should be recognized, however, that the observed persistence rates in controlled trials might not be reflective of 'real-life' clinical settings (see Andrade *et al.*, 1995). A recent study tracked prescription data at monthly intervals to assess the percentage of patients who continue on therapy during a 12-month period and noted that less than 20% of patients were still on their medication (oxybutynin and tolterodine IR and ER) at the end of 12 months (Chui *et al.*, 2004). This remarkably low persistence rate, attributable to poor efficacy and adverse effects, implies that we are still a long way from achieving our goal of delivering a medicine for OAB patients that offers a satisfactory balance of efficacy and tolerability over a chronic treatment period.

Conclusions

Despite impressive advances in our comprehension of the pathophysiology of the lower urinary tract, muscarinic receptor antagonism remains the only clinically proven mechanism for alleviating the symptoms of OAB. The recent regulatory approval of a number of new antimuscarinic molecules has expanded the therapeutic armamentarium for OAB. Emerging data from head-to-head clinical trials are revealing subtle differences in the clinical profile of these drugs. There is also greater clarity on the PK–PD relationship of these drugs. Nevertheless, modest efficacy and high incidence of dry mouth remain a common shortcoming of all drugs. Indeed, low persistence with therapy is a significant issue that limits the long-term benefit of antimuscarinic drugs. The combination of pharmacological and gene KO studies has solidified our understanding of the functional role of muscarinic receptor subtypes in the bladder. The findings from these studies, however, have not yet offered a clear discovery path for improving the therapeutic index of antimuscarinic molecules. There is still an unmet need for an antimuscarinic medicine with superior clinical effectiveness that can translate into better persistence on therapy.

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