Naunyn-Schmiedeberg's Arch Pharmacol (2013) 386:177–183
DOI 10.1007/s00210-012-0824-1

EDITORIAL

Pharmacological profile of β_3-adrenoceptor agonists in clinical development for the treatment of overactive bladder syndrome

Yasuhiko Igawa · Martin C. Michel

Received: 6 December 2012 / Accepted: 6 December 2012 / Published online: 21 December 2012

Abstract β_3-Adrenoceptor agonists are an emerging drug class for the treatment of the overactive bladder syndrome, and clinical proof-of-concept data have been obtained for three representatives of this class, mirabegron, ritobegron, and solabegron. We review here the pharmacological profile of these three drugs and discuss the potential clinical relevance of differences between them. In the absence of direct comparative studies, it appears that all three are strong agonists selective for β_3- vs. β_1- and β_2-adrenoceptors in studies with cloned receptor subtypes. The potency of these agonists may be species-dependent, with all three having high potency in the human detrusor. All three agonists were effective in one or more animal models of bladder dysfunction, which typically involved reductions of micturition frequency. Agonist doses effective for bladder function lowered blood pressure in some cases, but the relevance of this for clinical use is difficult to determine due to species differences in the importance of cardiovascular β_3-adrenoceptors. While limited effects on other organ systems are expected for β_3-adrenoceptor agonists, this requires further investigation.

Keywords Mirabegron · Ritobegron · Solabegron · Bladder

Introduction

The overactive bladder syndrome (OAB) is a prevalent condition among adults and occurs with increasing prevalence with advancing age. Currently, no cure is available for this condition, and present symptomatic treatment is based largely on conservative treatment and the use of muscarinic receptor antagonists. However, many patients experience insufficient therapeutic benefit and/or unpleasant side effects including dry mouth and constipation from muscarinic antagonists. Hence, few patients remain on treatment for longer than a few months. In the search for potential alternative OAB treatments, β_3-adrenoceptor agonists have emerged as a promising new drug class.

The potential of β_3-adrenoceptor agonists in OAB treatment is based on findings that the human bladder expresses β_3-adrenoceptors and that this is apparently the predominant if not exclusive β-adrenoceptor subtype mediating human detrusor relaxation; however, other subtypes may contribute to detrusor relaxation in other species such as rats (Michel and Vrydag 2006). Accordingly, β_3-adrenoceptor agonists have proven effective in a wide variety of animal models of OAB (Michel et al. 2011). Against this background, several selective β_3-adrenoceptor agonists have undergone clinical proof-of-concept studies including mirabegron (also known as YM 178), ritobegron (also known as KUC-7483 and as KUC-7322 for its active metabolite, which has primarily been used in the in vitro studies), and solabegron (also known as GW427353) (Fig. 1). Mirabegron has recently obtained regulatory approval in several countries. Therefore, we will shortly review the pharmacological profile of these three agonists and discuss needs for future pharmacological studies in this area.

Biochemical and cellular studies

To characterize the molecular interaction of the β_3-adrenoceptor agonists with their receptor, competition radioligand binding and cyclic AMP accumulation studies have been performed, primarily in cell lines transiently or stably

Y. Igawa
Department of Continence Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

M. C. Michel (✉)
Department of Pharmacology, Johannes Gutenberg University, Obere Zahlbacher Str. 67, 55101 Mainz, Germany
e-mail: martin.michel@boehringer-ingelheim.com

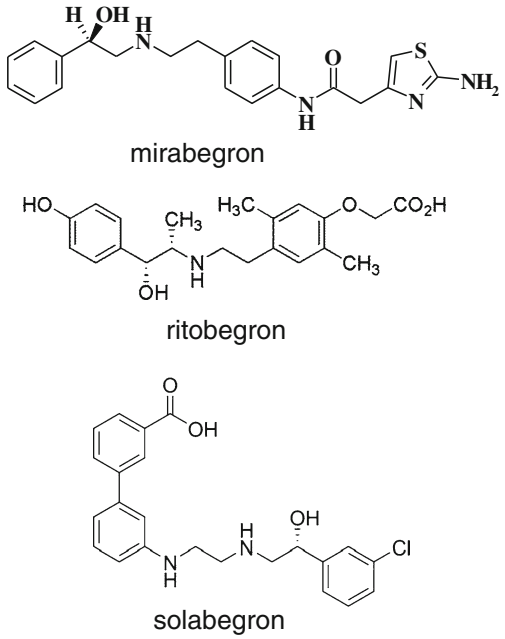

Fig. 1 Chemical structures of mirabegron, ritobegron (shown as active metabolite KUC-7322), and solabegron

transfected with the corresponding receptor. In Chinese hamster ovary (CHO) cells stably transfected with rat β_3-adrenoceptors, mirabegron stimulated cyclic AMP accumulation with an EC_{50} of 19 nM and an efficacy of 1.0 relative to that of isoprenaline; for β_1-adrenoceptors, an EC_{50} of 610 nM and an intrinsic efficacy of 0.6 was reported, whereas for β_2-adrenoceptors efficacy was <0.1 and potency could not be quantified (Hatanaka et al. 2013b). In CHO cells transfected with cynomolgus monkey β_3-adrenoceptors, mirabegron stimulated cAMP accumulation with an EC_{50} of 32 nM and an efficacy relative to isoprenaline of 0.8; the efficacy relative to isoprenaline at β_1- and β_2-adrenoceptors was only 0.2 and 0.1, respectively (Someya et al. 2010). Two studies on CHO cells transfected with human β-adrenoceptor subtypes were reported with rather similar results. Thus, mirabegron stimulated cyclic AMP accumulation via β_3-adrenoceptors with EC_{50} values of 22 nM (Takasu et al. 2007) and 1.5 nM (Hatanaka et al. 2013b), its efficacy relative to isoprenaline was 0.8 in both studies; in contrast, efficacy at human β_1- and β_2-adrenoceptors was only 0.1–0.2 in both studies, which did not allow quantification of potency. In human embryonic kidney (HEK) cells stably transfected with human β_3-adrenoceptors at a density of 121-fmol/mg protein, mirabegron and isoprenaline exhibited apparent affinities of 55 nM and 34 μM, respectively, in competition radioligand binding studies, and these affinities were not substantially altered in HEK cells transfected with several naturally occurring gene variants of the receptor (Vrydag et al. 2009). In cyclic AMP accumulation experiments in these HEK cells, mirabegron and isoprenaline exhibited EC_{50} values of 0.93 and 11.2 nM, respectively, and the efficacy of mirabegron relative to isoprenaline was 0.85, which is in good agreement with the findings in CHO cells (Hatanaka et al. 2013b; Takasu et al. 2007). The potency and efficacy of mirabegron also was not affected by genotype in these experiments. A 24-h pretreatment with 10 μM isoprenaline caused desensitization of the cyclic AMP response to freshly added isoprenaline or mirabegron, which primarily consisted of a reduced maximum response for both agonists (Vrydag et al. 2009); this desensitization also was independent of genotype.

The potency, efficacy, and selectivity of KUC-7322, the active metabolite of ritobegron, have been tested for cyclic AMP accumulation in CHO cells transiently transfected with each of the three human β-adrenoceptor subtypes (Maruyama et al. 2012a). These studies revealed EC_{50} values of 22,000, 2,300, and 73 nM for KUC-7322 at β_1-, β_2-, and β_3-adrenoceptors, respectively, as compared to 0.91, 0.67, and 12 nM, respectively, for isoprenaline. While KUC-7322 was a full agonist relative to isoprenaline at each of the three subtypes, its selectivity β_3- vs. β_1- or β_2-adrenoceptors was 301- and 32-fold, respectively.

Two series of experiments have been reported from stably transfected CHO cells measuring cyclic AMP accumulation via human β-adrenoceptor subtypes as stimulated by solabegron. In the first series, the EC_{50} of solabegron at human β_1-, β_2-, and β_3-adrenoceptors was 1,259, 3,981, and 3.98 nM, respectively, as compared to 1.0, 0.16, and 3.16 nM, respectively, for isoprenaline, i.e., solabegron was 1,000- and 316-fold selective for β_3- vs. β_1- or β_2-adrenoceptors (Uehling et al. 2006); in these experiments, the efficacy of solabegron relative to isoprenaline was 0.79 at β_3-adrenoceptors but 0.02 and 0.05 at β_1- or β_2-adrenoceptors, respectively. In a second series of experiments, solabegron stimulated cyclic AMP accumulation via human β_3-adrenoceptors with an EC_{50} of 6.9 nM as compared to 3.3 nM for isoprenaline, and the efficacy of solabegron relative to isoprenaline was 0.89 (Hicks et al. 2007). In these experiments in concentrations up to 10 μM, solabegron caused cyclic AMP accumulation of only 4.2 and 8.8 % of isoprenaline values at β_1- and β_2-adrenoceptors, respectively. Of note, this assay, if anything, had been biased against the detection of β_3-adrenoceptor agonism because β_1-, β_2-, and β_3-adrenoceptor expression densities were 1,070, 605, and 164 fmol/mg of protein, respectively.

Absolute potencies of the three β_3-adrenoceptor agonists are somewhat difficult to compare across studies due to differences in the cell lines, expression levels, and methods being used. However, it appears that mirabegron was slightly more potent than isoprenaline at human β_3-adrenoceptors, whereas KUC-7322 and solabegron were slightly less potent. Relative to isoprenaline, mirabegron, and solabegron were strong partial agonists with efficacies of 0.8–0.9,

whereas KUC-7322 appeared to be a full agonist. Whether these minor potency and efficacy differences are of clinical relevance remains unclear. Probably more importantly, all three agonists exhibited considerable selectivity over β_1- and β_2-adrenoceptors. However, mirabegron and solabegron had only poor efficacy at β_1- and β_2-adrenoceptors, whereas KUC-7322 had low potency but appeared to be a full agonist. These data imply that in vivo KUC-7322 may be more likely to activate β_1- or β_2-adrenoceptors than the other two agonists in tissues where a large receptor reserve exists, i.e., where occupation of only a small receptor fraction may already elicit a relevant response; however, this also remains to be tested experimentally as the receptor reserve in human atrium for β-adrenergic stimulation of inotropy is only small (Brown et al. 1992).

Isolated tissue studies

Isolated tissue experiments with β_3-adrenoceptor agonists in clinical development have largely been performed with isolated animal (rat, dog, and monkey) and human detrusor preparations (Table 1), but, in some cases, other tissues have also been examined. Similar to isoprenaline, mirabegron was somewhat more potent in human than in rat isolated bladder but, in both tissues, had an efficacy which was at least as large as that of isoprenaline (Takasu et al. 2007). In another study in rat bladder, a comparable potency of mirabegron was detected, but, in that study, the efficacy relative to isoprenaline was slightly smaller (Vrydag and Michel 2009). Another study has compared the potency and efficacy of mirabegron and isoprenaline in isolated detrusor strips obtained from patients without bladder dysfunction, bladder outlet obstruction, and bladder outlet obstruction with documented detrusor overactivity (Svalo et al. 2013). While mirabegron was consistently less potent than isoprenaline in all three groups, its efficacy was comparable to that of isoprenaline; while the potency of isoprenaline was significantly lower in patients with than without bladder outlet obstruction, smaller numerical differences between groups with mirabegron did not reach statistical significance. In the comparison of these data sets, it should be considered that some experiments were performed against carbachol-induced tone, whereas others were performed against KCl-induced tone; a previous work has demonstrated that β-adrenoceptor agonists generally are less potent and less effective against bladder contraction induced by muscarinic agonists than against that induced by KCl (Michel and Sand 2009; Witte et al. 2011).

The potency and efficacy of ritobegron, assessed by experiments with its active metabolite KUC-7322, for relaxation of rat bladder has been determined in three studies against passive tension (Maruyama et al. 2012a; Yamazaki et al. 2002) and (Cernecka et al. unpublished observations), and against carbachol- and KCl-induced tone in one study (Cernecka et al. unpublished observations). One of these studies demonstrated that the relaxing effects in rat bladder were not affected by co-application of the β_1-adrenoceptor antagonist CGP 20,712A and the β_2-adrenoceptor antagonist ICI 118,551 but inhibited when the β_3-adrenoceptor antagonist SR 58,894A was added on top of ICI 118,551, yielding an apparent pA_2 value of 6.43 for the latter, in line with the

Table 1 Potency and efficacy of selective β_3-adrenoceptor agonists for relaxation of isolated bladder preparations

Species	Mirabegron		Ritobegron		Solabegron	
	pEC_{50}	E_{max}, % of isoprenaline	pEC_{50}	E_{max}, % of isoprenaline	pEC_{50}	E_{max}, % of isoprenaline
Rat	5.29 (a)	120 (a)	7.14 (d)	n.r.	n.r	n.r.
	4.88 (b)	73 (b)	7.11 (e)	102 (e)		
	6.54 (c)	96 (c)	6.10 (f)	125 (f)		
			7.09 (g)	94 (g)		
			7.29 (h)	107 (h)		
Dog	n.r.	n.r.	n.r.	n.r.	>8 (m)	n.r.
Monkey	n.r.	n.r.	6.09 (i)	94 (i)	n.r.	n.r.
Human	6.11 (a)	104 (a)	5.94 (k)	100 (k)	n.r.	78 (n)
	6.23 (p)	98 (p)	5.92 (l)	87 (l)	8.73 (o)	n.r.

Data are based on (a) Takasu et al. (2007), (b) Vrydag and Michel (2009), (c) Hatanaka et al. (2013b), (d) Yamazaki et al. (2002), (e) Maruyama et al. (2012a), (f, g, and h) Cernecka et al. (unpublished observations), (i) Maruyama et al. (2012b), (k and l) Igawa et al. (2012), (m) Hicks et al. (2007), (n) Biers et al. (2006), (o) Tyagi et al. (2009), and (p) Svalo et al. (2013). Note that studies a, f, h, n, o, and p were performed against carbachol-induced contraction; studies b, g, l, and m, against KCl-induced contraction; and c, d, e, i, and k, against passive tension. Data for ritobegron refer to its active metabolite KUC-7322

n.r. not reported

relaxation response in rat bladder being solely mediated by β_3-adrenoceptors (Maruyama et al. 2012a). Across all of these studies, the potency ratio of isoprenaline/KUC-7322 was 8.1–29.5 (Table 1), whereas it was 80,000 for acceleration of rat atria beating rate and 2,200 for reduction of rat myometrial relaxation, representing prototypical β_1- and β_2-adrenoceptor responses, respectively (Maruyama et al. 2012a). Accordingly, KUC-7322 was much more potent in the rat bladder than in rat atrium and uterus, whereas the opposite was the case for isoprenaline. KUC-7322 also depressed spontaneous contractions of rat colon with an EC_{50} of 4.3 nM, and this was inhibited by SR 58,894A, indicating mediation via a β_3-adrenoceptor (Yamazaki et al. 2002). In the isolated cynomolgus monkey bladder, both KUC-7322 and isoprenaline were less potent than in the rat, but KUC-7322 remained a full agonist (Maruyama et al. 2012b). Similar to the rat studies, KUC-7322 was considerably more potent for bladder relaxation than atrial beating rate or tracheal relaxation in the monkey, whereas, if anything, the opposite was true for isoprenaline (Maruyama et al. 2012b). In isolated human bladder, KUC-7322 was slightly less potent than in the monkey bladder and much less potent than in the rat bladder in two independent studies performed against either passive tension of KCl-induced tone but remained a full agonist relative to isoprenaline (Igawa et al. 2012). The response against KCl-induced tone was not affected by the β_1-adrenoceptor antagonist CGP 20,712A or the β_2-adrenoceptor antagonist ICI 118,551,but surprisingly also not by the general β-adrenoceptor antagonist SR 59,230A (Niclauß et al. 2006).

In contrast to the other agonists, bladder relaxation by solabegron has not been reported in rats as the primary animal species but has been in dogs (Hicks et al. 2007). In this species, solabegron caused concentration-dependent relaxation against KCl-induced tone, but a smaller but substantial relaxation was also seen in time control experiments with vehicle addition. While solabegron caused significantly greater relaxation than vehicle, this made quantitative analysis of the solabegron concentration–response curve difficult; however, it appears that the EC_{50} of solabegron in isolated dog bladder was <10 nM. In single-concentration experiments, relaxation by solabegron was not affected by the β_1-selective atenolol or the β_2-selective ICI 118,551 but attenuated by the non-selective antagonist bupranolol. The non-selective antagonist SR 59,230A (Niclauß et al. 2006) attenuated the response to solabegron but also caused some relaxation in the absence of solabegron (Hicks et al. 2007). Relaxation responses to SR 59,230A in the absence of exogenous agonist had also been reported in rat and human bladder (Frazier et al. 2011). In one study with isolated human bladder strips, solabegron produced concentration-dependent relaxation with an efficacy comparable with that of isoprenaline, but the resulting curves did not allow calculation of an EC_{50} value (Biers et al. 2006); in that study, SR 59,230A produced a right shift of the solabegron concentration–response curve. Within that study, spontaneous contractile activity was also noted in some strips and that was also reduced by solabegron. Moreover, solabegron also inhibited field stimulation-induced contraction, which was not mimicked by isoprenaline. In another study with human isolated detrusor strips, solabegron produced relaxation with an EC_{50} of 1.9 nM with an efficacy similar to that of isoprenaline (Tyagi et al. 2009). Within that study, both solabegron and isoprenaline also inhibited human detrusor tone induced by field stimulation.

In conclusion, mirabegron appears to be somewhat more potent in the human as compared to rodent bladder, whereas the opposite may be the case of the active metabolite of ritobegron. In the human bladder, solabegron (potency in rodents not reported) appears to be more potent than mirabegron and ritobegron. All three agonists appear to have an efficacy comparable to that of isoprenaline (Table 1).

In vivo animal studies

Several in vivo studies have been reported for each of the three agonists, mainly with regard to bladder function. In the urethane-anesthetized rat, i.v. administration of mirabegron produced a dose-dependent reduction in the frequency of rhythmic bladder contractions but did not significantly decrease contraction amplitude in doses up to 3 mg/kg; in contrast, the muscarinic antagonist oxybutynin increased contraction frequency and reduced contraction amplitude (Takasu et al. 2007). In pentobarbital-anesthetized rats, i.v. administration of mirabegron dose-dependently reduced intravesicular pressure and spontaneous bladder contractions; this was accompanied by a dose-dependent heart rate increase of up to 11 % and a mean blood pressure decrease of up to 29 % (Hatanaka et al. 2013a). In rats with cerebral infarction-induced bladder dysfunction, mirabegron dose-dependently increased voided volume and partly normalized it (Hatanaka et al. 2013b). In rats with bladder outlet obstruction, i.v. administration of mirabegron reduced the frequency of non-voiding bladder contractions but did not affect voiding contractions, micturition pressure, threshold pressure, voided volume, residual volume, or bladder capacity (Hatanaka et al. 2013a). Within that study, oxybutynin or tolterodine did not affect the frequency of non-voiding contractions, but oxybutynin significantly increased residual volume, and tolterodine reduced voided volume. In another study in rats with bladder outlet obstruction, non-voiding activity consisted of small and large transients and i.v. administration of both mirabegron and tolterodine reduced the cumulative activity of the large non-voiding contractions but had little effect on the small transients (Gillespie et al. 2012). In that study, mirabegron primarily reduced the

frequency of such contractions, whereas tolterodine mainly reduced their amplitude. The authors proposed a model in which both agents act on a pacemaker-like mechanism with cholinergic excitatory and adrenergic inhibitory inputs. In water-loaded, conscious cynomolgus monkeys, oral mirabegron at 1–3 mg/kg reduced micturition frequency and increased voided volume per micturition but did not affect total voided volume (Someya et al. 2010). To improve the mechanistic understanding on mirabegron effects in the bladder, a study was performed in urethane-anesthetized rats in which single-unit mechanosensitive bladder afferent Aδ- and C-fiber activities (identified based upon conduction velocities) were identified at the L6 dorsal root by electrical stimulation of the pelvic nerve and bladder distension (Aizawa et al. 2012). Mirabegron dose-dependently inhibited mechanosensitive bladder afferent activities of both Aδ- and C-fibers during bladder filling, which was more remarkable for Aδ-fibers. In addition, under isovolumetric conditions of the bladder, mirabegron inhibited both the bladder microcontractions and Aδ-fiber activity at doses that did not decrease the bladder pressure. At higher doses, which also decreased the bladder pressure, mirabegron inhibited C-fiber activity. These effects were not observed with oxybutynin.

Intraduodenal administration of ritobegron or i.v. administration of its active metabolite KUC-7322 dose-dependently reduced intravesicular pressure in urethrane-anesthetized male rats (Maruyama et al. 2012a; Yamazaki et al. 2002); within these studies, ritobegron did not affect heart rate and reduced blood pressure by about 10 mm Hg. In conscious female rats in which bladder irritation was induced by intravesical prostaglandin E_2 instillation, intragastric administration of ritobegron prolonged the micturition interval and increased the micturition volume (Yamazaki et al. 2002). In enflurane-anesthetized cynomolgus monkeys intraduodenal administration of ritobegron dose-dependently reduced intravesicular pressure without significantly affecting heart rate or mean blood pressure, whereas i.v. administration of isoprenaline after ritobegron increased heart rate and reduced blood pressure (Maruyama et al. 2012b).

The originally reported in vivo data with solabegron relate to its potential for the treatment of type 2 diabetes and/or obesity. Thus, a 14-day oral treatment of db/db mice with solabegron dose-dependently lowered plasma glucose, HbA1c, and insulin levels and elicited a thermogenic response from the brown fat-rich interscapular region (Uehling et al. 2006). Given the differential role of β_3-adrenoceptors in glucose and lipid metabolism between rodents and humans (Arch 2008), the relevance of such findings for OAB patients is difficult to predict. In a placebo-controlled, double-blind study in 36 healthy volunteers, oral administration of solabegron doses of 50 or 200 mg twice daily for 7 days did not significantly alter gastrointestinal or colonic transit or bowel function (Grudell et al. 2008). In propofol-anesthetized female dogs, bladder irritation was induced by intravesical acetic acid instillation; in this model, i.v. administration of solabegron increased micturition volume threshold but did not significantly affect voided volume, voiding efficiency, bladder contraction amplitude, and duration (Hicks et al. 2007). Within that study, the solabegron dose increasing micturition volume threshold decreased mean arterial pressure by 35 mm Hg and increased heart rate by 97 bpm. Pretreatment of the dogs with the antagonist bupranolol significantly attenuated the solabegron effects on micturition volume threshold and heart rate but not those on mean arterial pressure.

In conclusion, all three agonists have proven efficacious in one or more in vivo bladder function models. The differences in models being used make comparisons across compounds difficult. It is noteworthy that in doses effective on the bladder, ritobegron had little effect on cardiovascular function in monkeys, whereas as mirabegron and solabegron lowered blood pressure and increased heart rate in rats and dogs, respectively. However, it should be noted that the role of β_3-adrenoceptors in cardiovascular regulation may be highly species-dependent (Rozec and Gauthier 2006), which implies that comparisons between species and models are difficult, and cardiovascular effects in experimental animals do not necessarily predict their presence in humans.

Perspective

While the above studies already provide considerable insight into the pharmacological properties of selective β_3-adrenoceptor agonists currently in clinical development, a number of questions remain to be answered for a more comprehensive characterization of these compounds and the entire drug class. For example, the effects of β_3-adrenoceptor agonists at the cellular level have mostly been studied using cAMP formation/accumulation as a functional read-out. However, it has now become clear that β-adrenoceptors in general and β_3-adrenoceptors in particular can couple to multiple signaling pathways and that some ligands preferentially activate some of these pathways as compared to others, a phenomenon called "biased agonism" or "ligand-directed signaling" (Evans et al. 2010). Whether and how mirabegron, ritobegron ,and solabegron are affected by this phenomenon remains to be studied.

While most of the in vitro bladder function studies with β_3-adrenoceptor agonists have looked at smooth muscle function, some of the in vivo findings already indicate that afferent nerves may also contribute to their overall profile. While β_3-adrenoceptors are also expressed in human urothelium (Ochodnicky et al. 2012), it remains controversial whether such receptors contribute to β_3-adrenoceptor agonist effects on detrusor function (Kullmann et al. 2011; Masunaga et al. 2010; Propping et al. 2009). Other potential effects of

β_3-adrenoceptor agonists on bladder function should also be considered. For example, there is an interaction between muscarinic and β-adrenergic systems in the bladder (Witte et al. 2011), which may be important pathophysiologically when acetylcholine is released non-neuronally during the storage phase but also therapeutically if a combination treatment of muscarinic antagonists and β-adrenergic agonists is being considered. In this regard, we are still trying to understand why some muscarinic antagonists exhibit a certain degree of bladder selectivity (Yamazaki et al. 2011), and it is largely unknown whether a similar phenomenon exists for β_3-adrenoceptor agonists. Moreover, it is well established that the function of the systemic renin–angiotensin system is in part regulated by β-adrenoceptors, in humans β_1-adrenoceptors, but a local renin–angiotensin system also exists in the urogenital tract (Comiter 2012). β-Adrenoceptors are also known to affect the function of gap junctions in the heart (Salameh and Dhein 2011), and gap junctions also play a role in the regulation of bladder function (Roosen et al. 2009). Moreover, adrenergic agonists can affect expression of uroplakin in the bladder, and this may play a role in cystitis (Kyung et al. 2012). A potential role of β_3-adrenoceptors in all of these effects has not yet been explored. Such work will be added by a better characterization of the localization of expression of β_3-adrenoceptors in the bladder and other tissues, but tools to characterize such expression at the protein level are just emerging (Cernecka et al. 2012). Finally, some of the above studies have already explored β_3-adrenoceptor agonist effects outside the bladder as a potential source of side effects, but they may also be leading to potential future indication, e.g., with retinal disease (Mori et al. 2011). Thus, plenty of research remains to be done to obtain a more complete picture of β_3-adrenoceptor agonist pharmacology.

Acknowledgments Work in the authors' labs has been supported in part by a Grant-in-Aid for Scientific Research (grant no. 23592358) from the Ministry of Education, Culture, Sport, Science and Technology of the Japanese Government and by Coordination Theme 1 (Health) of the European Community's FP7, grant agreement number HEALTH-F2-2008-223234. In the field of β_3-adrenoceptor research, YI has received research support from Astellas and Kissei and has been a consultant Astellas and Pfizer. MCM has received research support, consultancy, and/or lecturer honoraria from AltherRx, Astellas, Boehringer Ingelheim; he currently is an employee of Boehringer Ingelheim.

References

Aizawa N, Homma Y, Igawa Y (2012) Effects of mirabegron, a novel β_3-adrenoceptor agonist, on the primary bladder afferent activity and bladder microcontractions in rats in comparison with those of oxybutynin. Eur Urol 62:1166–1173

Arch JRS (2008) Perspectives from β_3-adrenoceptor agonists on pharmacology, physiology and obesity drug discovery. Naunyn-Schmiedeberg's Arch Pharmacol 378:225–240

Biers SM, Reynard JM, Brading AF (2006) The effects of a new selective β_3-adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder. BJU Int 98:1310–1314

Brown L, Deighton NM, Bals S, Söhlmann W, Zerkowski H-R, Michel MC, Brodde O-E (1992) Spare receptors for β-adrenoceptor-mediated positive inotropic effects of catecholamines in the human heart. J Cardiovasc Pharmacol 19:222–232

Cernecka H, Ochodnicky P, Lamers WH, Michel MC (2012) Specificity evaluation of antibodies against human β_3-adrenoceptors. Naunyn-Schmiedeberg's Arch Pharmacol 385:875–882

Comiter C (2012) Local renin-angiotensin systems in the genitourinary tract. Naunyn-Schmiedeberg's Arch Pharmacol 385:13–26

Evans BA, Sato M, Sarwar M, Hutchinson DS, Summers RJ (2010) Ligand-directed signalling at β-adrenoceptors. Br J Pharmacol 159:1022–1038

Frazier EP, Michel-Reher MB, van Loenen P, Sand C, Schneider T, Peters SLM, Michel MC (2011) Lack of evidence that nebivolol is a β_3-adrenoceptor agonist. Eur J Pharmacol 654:86–91

Gillespie JI, Palea S, Guilloteau V, Guerard M, Lluel P, Korstanje C (2012) Modulation of non-voiding activity by the muscarinergic antagonist tolterodine and the β_3-adrenoceptor agonist mirabegron in conscious rats with partial outflow obstruction. BJU Int 110:E132–E142

Grudell ABM, Camilleri M, Jensen KL, Foxx-Orenstein AE, Burton DD, Ryks MD, Baxter KL, Cox DS, Dukes GE, Kelleher DL, Zinsmeister AR (2008) Dose–response effect of a β_3-adrenergic receptor agonist, solabegron, on gastrointestinal transit, bowel function, and somatostatin levels in health. Am J Physiol 294: G1114–G1119

Hatanaka T, Ukai M, Watanabe M, Someya A, Ohtake A, Suzuki M, Ueshima K, Sato S, Kaku S (2013a) Effect of mirabegron, a novel β_3-adrenoceptor agonist, on bladder function during storage phase in rats. Naunyn-Schmiedeberg's Arch Phamacol. doi:10.1007/s00210-012-0814-3

Hatanaka T, Ukai M, Watanabe M, Someya A, Ohtake A, Suzuki M, Ueshima K, Sato S, Sasamata M (2013b) In vitro and in vivo pharmacological profile of a selective β_3-adrenoceptor agonist mirabegron in rats. Naunyn-Schmiedeberg's Arch Pharmacol. doi:10.1007/s00210-012-0821-4

Hicks A, McCafferty GP, Riedel E, Aiyar N, Pullen M, Evans C, Luce TD, Coatney RW, Rivera GC, Westfall TD, Hieble JP (2007) GW427353 (solabegron), a novel, selective β_3-adrenergic receptor agonist, evokes bladder relaxation and increases micturition reflex threshold in the dog. J Pharmacol Exp Ther 323:202–209

Igawa Y, Schneider T, Yamazaki Y, Tatemichi S, Homma Y, Nishizawa O, Michel MC (2012) Functional investigation of β-adrenoceptors in human isolated detrusor focusing on the novel selective β_3-adrenoceptor agonist KUC-7322. Naunyn-Schmiedeberg's Arch Pharmacol 385:759–767

Kullmann FA, Downs TR, Artim DE, Limberg BJ, Shah M, Contract D, De Groat WC, Rosenbaum JS (2011) Urothelial beta-3 adrenergic receptors in the rat bladder. Neurourol Urodyn 30:144–150

Kyung YS, Park H, Lee G (2012) Intravesical epinephrine preserves uroplakin II expression in urinary bladder from cyclophosphamide-induced rat cystitis. Naunyn-Schmiedeberg's Arch Pharmacol 385:769–776

Maruyama I, Goi Y, Tatemichi S, Maruyama K, Hoyano Y, Yamazaki Y, Kusama H (2012a) Bladder selectivity of ritobegron (KUC-7483), a novel β_3-adrenoceptor agonist: on the in vitro and in vivo studies. Naunyn-Schmiedeberg's Arch Pharmacol 385:845–852

Maruyama I, Tatemichi S, Goi Y, Maruyama K, Hoyano Y, Yamazaki Y, Kusama H (2012b) Effects of ritobegron (KUC-7483), a novel selective β_3-adrenoceptor agonist, on bladder function in cynomolgus monkey. J Pharmacol Exp Ther 342:163–168

Masunaga K, Chapple CR, McKay NG, Yoshida M, Sellers DJ (2010) The β_3-adrenoceptor mediates the inhibitory effects of β-adrenoceptor agonists via the urothelium in pig bladder dome. Neurourol Urodyn 29:1320–1325

Michel MC, Sand C (2009) Effect of pre-contraction on β-adrenoceptor-mediated relaxation of rat urinary bladder. World J Urol 27:711–715

Michel MC, Vrydag W (2006) α_1-, α_2- and β-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol 147: S88–S119

Michel MC, Ochodnicky P, Homma Y, Igawa Y (2011) β-Adrenoceptor agonist effects in experimental models of bladder dysfunction. Pharmacol Ther 131:40–49

Mori A, Nakahara T, Sakamoto K, Ishii K (2011) Role of β_3-adrenoceptors in regulation of retinal vascular tone in rats. Naunyn-Schmiedeberg's Arch Pharmacol 384:603–608

Niclauß N, Michel-Reher MB, Alewijnse AE, Michel MC (2006) Comparison of three radioligands for the labelling of human β-adrenoceptor subtypes. Naunyn-Schmiedeberg's Arch Pharmacol 374:79–85

Ochodnicky P, Humphreys S, Eccles R, Poljakovic M, Wiklund P, Michel MC (2012) Expression profiling of G-protein-coupled receptors in human urothelium and related cell lines. BJU Int 110:e293–e300

Propping S, Wuest M, Eichhorn B, Grimm M, Wirth M, Kaumann A, Ravens U (2009) Role of urothelium on β_3-adrenoceptor mediated relaxation in human detrusor muscle. Neurourol Urodyn 28: 870–871

Roosen A, Chapple CR, Dmochowski RR, Fowler CJ, Gratzke C, Roehrborn CG, Stief CG, Andersson K-E (2009) A refocus on the bladder as the originator of storage lower urinary tract symptoms: a systematic review of the latest literature. Eur Urol 56: 810–820

Rozec B, Gauthier C (2006) β_3-Adrenoceptors in the cardiovascular system: putative roles in human pathologies. Pharmacol Ther 111:652–673

Salameh A, Dhein S (2011) Adrenergic control of cardiac gap junction function and expression. Naunyn-Schmiedeberg's Arch Pharmacol 383:331–346

Someya A, Ukai M, Yanai H, Watanabe M, Ohtake A, Ueshima K, Suzuki M, Sato S, Sasamata M (2010) Mirabegron (YM178), a novel β_3-adrenoceptor (AR) agonist, increased functional bladder capacity and decreased micturition frequency in conscious water-loaded cynomolgus monkeys. Eur Urol Suppl 9:111

Svalo J, Nordling J, Bouchelouche K, Andersson K-E, Korstanje C, Bouchelouche P (2013) The novel β_3-adrenoceptor agonist mirabegron reduces carbachol-induced contractile activity in detrusor tissue from patients with bladder outflow obstruction with or without detrusor overactivity. Eur J Pharmacol doi:10.1016/j.ejphar.2012.11.060

Takasu T, Ukai M, Sato S, Matsui T, Nagase I, Maryama T, Sasamata M, Miyata K, Uchida H, Yamaguchi O (2007) Effect of YM178, a novel selective β_3-adrenoceptor agonist, on bladder function. J Pharmacol Exp Ther 321:642–647

Tyagi P, Thomas CA, Yoshimura N, Chancellor MB (2009) Investigations into the presence of functional β1, β2 and β_3-adrenoceptors in urothelium and detrusor of human bladder. Int Braz J Urol 35:76–83

Uehling DE, Shearer BG, Donaldson KH, Chao EY, Deaton DN, Adkison KK, Brown KK, Cariello NF, Faison WL, Lancaster ME, Lin J, Hart R, Milliken TO, Paulik MA, Sherman BW, Sugg EE, Cowan C (2006) Biarylaniline phenethanolamines as potent and selective β_3 adrenergic receptor agonists. J Med Chem 49:2758–2771

Vrydag W, Michel MC (2009) Agonist-dependent desensitization of the β-adrenoceptor-mediated rat urinary bladder relaxation. pA2 online 6: www.pA2online.org/abstracts/Vol6Issue4abst041.pdf

Vrydag W, Alewijnse AE, Michel MC (2009) Do gene polymorphisms alone or in combination affect the function of human β_3-adrenoceptors? Br J Pharmacol 156:127–134

Witte LPW, de Haas N, Mammen M, Stangeland EL, Steinfeld T, Aiyar J, Michel MC (2011) Muscarinic receptor subtypes and signalling involved in the attenuation of isoprenaline-induced rat urinary bladder relaxation. Naunyn-Schmiedeberg's Arch Pharmacol 384:555–563

Yamazaki Y, Tatemichi S, Maruyama I, Takeda H, Kaidoh K, Kojima M, Akahane S, Shibata N, Akahane M (2002) Characterization of KUC-7483 and its active metabolite, KUC-7322, a selective beta3-adrenoceptor agonist, on bladder function in rats. https://www.icsofficeorg/publications/2002/pdf/095.pdf

Yamazaki T, Muraki Y, Anraku T (2011) In vivo bladder selectivity of imidafenacin, a novel antimuscarinic agent, assessed by using an effectiveness index for bladder capacity in rats. Naunyn-Schmiedeberg's Arch Pharmacol 384:319–329