1. Introduction

Voiding function, which consists of the storage and excretion of urine, is modulated by the sympathetic, parasympathetic, and somatic nervous systems. Normal micturition reflex is controlled by a balance of contraction and relaxation of the lower urinary tract, and imbalance is known to induce a variety of voiding dysfunctions.

Overactive bladder (OAB) syndrome is characterized by urgency with or without urge incontinence, usually accompanied by daytime frequency and nocturia. The cornerstone symptom is urgency, which can be described as a sudden compelling desire to pass urine that is difficult to defer (1). The urgency is considered to drive other OAB symptoms. Although OAB symptoms do not directly threaten the lives of people, the condition has a profoundly negative effect on the quality of life (QOL) of those affected. While the pathogenic mechanisms of OAB are multifactorial, a main cause is considered to be involuntary bladder contraction. The most widely used therapy for OAB is thus muscarinic receptor antagonists.

In urinary bladder, acetylcholine (ACh) released from postganglionic parasympathetic nerve terminals activates postjunctional muscarinic receptors. Five muscarinic

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Abstract. Overactive bladder (OAB) syndrome is a common condition that is most often observed in the elderly. Pharmacological treatment with muscarinic receptor antagonists has been most widely used for OAB. An antimuscarinic agent, solifenacin, showed the highest affinity for the muscarinic M3 receptor, which mediates urinary bladder contraction. In preclinical studies, solifenacin exhibited a highly bladder-selective profile compared with other antimuscarinic agents. Solifenacin was also shown to increase bladder capacity without affecting residual urine in an OAB model of rats. Urgency is now considered to result from overactivation of afferent nerves from the urinary bladder. It has been reported that afferent nerves are located adjacent to the urothelium, and stimulation of muscarinic receptors expressed on the urothelium may contribute to the activation of afferent nerves via non-neuronal ATP release. Solifenacin produces its inhibitory effect on bladder afferent activity partly via the suppression of non-neuronal ATP release. Clinically, solifenacin ameliorates all symptoms in OAB patients; and in particular, it produces a significant decrease in urgency episodes, which is the principal symptom of OAB. The pharmacological profile of solifenacin is therefore considered to contribute to its beneficial effects of high efficacy against OAB symptoms with good tolerability.

Keywords: solifenacin, muscarinic receptor, overactive bladder, urgency, afferent nerve, lower urinary tract
receptor subtypes (M₁ – M₅) have been identified by both molecular biological and pharmacological investigations. Urinary bladder smooth muscle contains a mixed population of M₂ and M₁ receptors. Although M₂ receptors are numerically predominant, M₃ receptors are considered to be involved in the mediation of bladder contraction (2). It has been reported that stretching of human urinary bladder results in the release of non-neuronal ACh from urothelium (3). This non-neuronal ACh is considered to be involved in overactivity of the urinary bladder via activation of afferent C-fibers. Muscarinic receptors are expressed in the urothelium, and the stimulation of non-neuronal ACh induces the release of non-neuronal adenosine triphosphate (ATP) (4). This non-neuronal ATP is also considered to activate the afferent pathway. This activation of the afferent pathway is involved in the pathogenesis of urgency, which is in turn followed by the other symptoms of OAB.

The muscarinic M₁ receptor is the predominant subtype not only in urinary bladder but also in submandibular gland, where it regulates salivary secretion (5). Antimuscarinic agents thus produce dry mouth as an adverse effect, which is the main reason for the discontinuation of these agents. Antimuscarinic agents with a lesser effect on salivary secretion have therefore been sought. Against this background, Astellas Pharma, Inc. instituted a program with the aim of discovering bladder-selective antimuscarinic agents, which resulted in the discovery of solifenacin succinate in 1996. The beneficial effect of solifenacin (Vesicare®) on the symptoms of OAB has been confirmed in a number of clinical studies, and the product was launched for the indication of OAB in Europe in 2004, the USA in 2005, and Japan in 2006 (6, 7). This review summarizes the pharmacological profile of solifenacin for muscarinic receptors, voiding function, bladder selectivity, and bladder afferent pathways and attempts to relate this to clinical data in OAB patients, in which the urgency episodes were used as the primary endpoint.

2. Pharmacological characteristics

2.1. Effects on muscarinic receptors

In binding assays using human muscarinic receptors, it was confirmed that the affinity of solifenacin for the muscarinic M₃ receptor (Kᵣ value of 12 nM) was 2.2-, 15-, 9.1-, and 2.6-fold higher than those for M₁, M₂, M₄, and M₅ receptors, respectively (8). Solifenacin thus showed the highest affinity for the M₃ receptor, which mediates urinary bladder contraction.

Drugs possessing M₂-receptor antagonism will increase heart rate by blocking the M₂ receptor of the heart. However, since solifenacin has a low affinity for the M₂ receptor, it is considered that adverse effects such as tachycardia are of little concern. Learning and memory processes in the central nervous system are thought to be primarily the responsibility of the M₁-receptor subtype (9). Although the affinity of solifenacin for the M₃ receptor is only marginal over that for the M₁-receptor subtype, solifenacin was scarcely detected in the brain of rats, indicating that it does not penetrate the blood-brain barrier (10). In addition, it was confirmed that solifenacin does not affect learning function in a passive avoidance task in rats (11). Adverse effects such as impairment of cognitive functions are therefore considered of little concern.

Further, solifenacin has been confirmed to have little effect on a range of ion channels and receptors other than muscarinic receptors.

In isolated rat urinary bladder strips, solifenacin shifted the concentration–contraction curves of carbachol to the right in a concentration-dependent manner with a pD₂ value of 7.4, and the Schild slope was not significantly different from unity, suggesting that the antagonistic effect on the M₃ receptor is competitive (8).

2.2. Effect on bladder function

Cerebral infarction is known to induce detrusor overactivity in rats via the impairment of suppression pathways of the micturition reflex and is used widely as a model of OAB (12). The effect of solifenacin on bladder function was investigated using a cystometry method in this rat model (13).

Cerebral infarcted rats exhibited decreases in bladder capacity and voided volume and an increase in residual volume, but no change in micturition pressure (Fig. 1). Solifenacin increased bladder capacity and voided volume without affecting micturition pressure or residual volume (Fig. 1).

2.3. Bladder-selectivity profile

2.3.1. In vitro

The effects of antimuscarinic agents on increases in intracellular Ca²⁺ levels by the muscarinic receptor agonist carbachol were investigated in bladder smooth muscle cells and salivary gland cells isolated from rats and cynomolgus monkeys.

Solifenacin inhibited carbachol-induced increases in intracellular Ca²⁺ levels in bladder smooth muscle cells and salivary gland cells isolated from rats in a concentration-dependent manner (14, 15). The inhibitory potency for bladder smooth muscle cells was significantly greater than that for submandibular gland cells. Solifenacin showed 3.6-fold selectivity for bladder, calculated as the ratio of affinity constants in urinary bladder over submandibular gland (Table 1). Other antimuscarinic agents
such as tolterodine, imidafenacin, oxybutynin, and propiverine also inhibited increases in intracellular Ca$^{2+}$ levels in both cells, but with 2.0-, 1.1-, 2.1-, and 1.3-fold greater bladder selectivity, respectively.

Solifenacin inhibited carbachol-induced increases in intracellular Ca$^{2+}$ levels in bladder smooth muscle cells and salivary gland cells isolated from the same cynomolgus monkeys in a concentration-dependent manner (16). Inhibitory potency for bladder smooth muscle cells was significantly greater than that for submandibular gland cells, showing 2.1-fold greater bladder selectivity. Although tolterodine and oxybutynin also inhibited increases in intracellular Ca$^{2+}$ levels in both cells, their bladder selectivity was significantly lower than that of solifenacin.

### 2.3.2. In vivo

The effects of antimuscarinic agents on carbachol-induced increases in intravesical pressure and salivary secretion were investigated in anesthetized rats (14, 15).

Solifenacin inhibited carbachol-induced increases in intravesical pressure and salivary secretion, with significantly greater inhibitory potency for urinary bladder than salivary gland (Fig. 2). From a comparison of the ID$_{30}$ or

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**Table 1.** Antagonist affinity constants ($pK_i$) of antimuscarinic agents for carbachol-induced intracellular Ca$^{2+}$ mobilization in bladder smooth muscle cells and submandibular gland cells isolated from rats

<table>
<thead>
<tr>
<th></th>
<th>Bladder smooth muscle cells (B)</th>
<th>Submandibular gland cells (S)</th>
<th>Bladder selectivity (S/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacin</td>
<td>8.12 ± 0.04**</td>
<td>7.57 ± 0.06</td>
<td>3.6</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>8.55 ± 0.05**</td>
<td>8.26 ± 0.07</td>
<td>2.0</td>
</tr>
<tr>
<td>Imidafenacin</td>
<td>8.76 ± 0.04</td>
<td>8.74 ± 0.10</td>
<td>1.1</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>8.75 ± 0.05**</td>
<td>8.43 ± 0.08</td>
<td>2.1</td>
</tr>
<tr>
<td>Propiverine</td>
<td>6.61 ± 0.07</td>
<td>6.50 ± 0.04</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E.M. of five separate experiments. Significant differences between $pK_i$ values of bladder smooth muscle cells and submandibular gland cells were seen for each drug tested (**$P < 0.01$, Student’s t-test). All data are reproduced from refs. 14 and 15 with permission from Elsevier (©2004) and Life Science Publishing, Co., Ltd. (©2008), respectively.
ID$_{50}$ values, the doses required to induce 30% and 50% inhibition of the baseline value, respectively, solifenacin showed 6.5- and 3.7-fold greater selectivity for urinary bladder over salivary gland, respectively (Table 2), and at ID$_{30}$ or higher values increased bladder capacity and voided volume in cerebral infarcted rats (Fig. 1). In contrast, tolterodine also showed 2.4- and 2.2-fold greater selectivity for urinary bladder over salivary gland, respectively, while imidafenacin, oxybutynin, and propiverine showed no functional selectivity for urinary bladder (0.97- to 1.6-fold) (Table 2).

In addition, the selectivity of urinary bladder to the brain region of antimuscarinic agents in rats was also evaluated by ratios for the brain receptor occupancy to the pharmacological potency in the urinary bladder. The selectivity for the urinary bladder over the brain was...
Effect of Solifenacin on Urgency Episodes

139

Table 2. Inhibitory effects of antimuscarinic agents on carbachol-induced intravesical pressure elevation and salivary secretion in anesthetized rats

<table>
<thead>
<tr>
<th></th>
<th>ID_{50} value (95% confidence limits)</th>
<th>Bladder selectivity (S/B)</th>
<th>ID_{50} value (95% confidence limits)</th>
<th>Bladder selectivity (S/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intravesical pressure elevation (B)</td>
<td>Salivary secretion (S)</td>
<td>Intravesical pressure elevation (B)</td>
<td>Salivary secretion (S)</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>0.023 (0.010 – 0.039)</td>
<td>0.15 (0.11 – 0.24)</td>
<td>6.5</td>
<td>0.11 (0.08 – 0.14)</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>0.010 (0.008 – 0.014)</td>
<td>0.024 (0.016 – 0.047)</td>
<td>2.4</td>
<td>0.026 (0.021 – 0.033)</td>
</tr>
<tr>
<td>Imidafenacin</td>
<td>0.00043 (0.00023 – 0.00130)</td>
<td>0.00070 (0.00056 – 0.00084)</td>
<td>1.6</td>
<td>0.0012 (0.0009 – 0.0016)</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>0.027 (0.015 – 0.045)</td>
<td>0.030 (0.024 – 0.038)</td>
<td>1.1</td>
<td>0.067 (0.050 – 0.090)</td>
</tr>
<tr>
<td>Propiverine</td>
<td>0.68 (0.28 – 1.2)</td>
<td>0.75 (0.36 – 1.3)</td>
<td>1.1</td>
<td>1.6 (1.1 – 2.5)</td>
</tr>
</tbody>
</table>

ID_{30} and ID_{50} values (mg/kg, i.v.) are the doses required to induce 30% and 50% inhibition from baseline values, respectively, and were determined by linear regression analysis (n = 6). All data are reproduced from refs. 14 and 15 with permission from Elsevier (©2004) and Life Science Publishing, Co., Ltd. (©2008), respectively.

greater for solifenacin than oxybutynin (10).

Although solifenacin has shown greater selectivity for urinary bladder over salivary gland than other antimuscarinic agents in both in vitro and in vivo studies, the reason for this difference may be difficult to explain in terms of muscarinic receptor–subtype selectivity only. The inhibitory effect of solifenacin on salivary secretion was recently reported to be weaker than that of oxybutynin in mice, due to solifenacin’s slower receptor binding kinetics of association and lower binding activity than oxybutynin (17, 18). In addition, solifenacin dissociates more readily from muscarinic receptors in the mouse submaxillary gland than oxybutynin, which is also considered to contribute to its weak inhibitory effect on salivary secretion. However, further studies are required to determine details of the mechanism of solifenacin’s bladder selectivity.

2.4. Effect on bladder afferent pathways

As mentioned above, intravenous solifenacin dose-dependently increased bladder capacity in cerebral infarcted rats. This effect was partly suppressed by treatment with resiniferatoxin, which desensitizes afferent C-fibers (19). Intravenous solifenacin has been reported to reduce the bladder afferent activity with the measurement of pelvic nerve spikes in rats (20). In addition, bladder instillation of carbachol induced decreases in bladder capacity, and intravesical human urine obtained after administration of solifenacin prevented carbachol-induced decreases in bladder capacity (21). In contrast, intravesical human urine obtained after administration of tolterodine and darifenacin showed no effect on bladder function. This difference is considered to be attributed to the percentage of the intact compound excreted in the urine. It is therefore considered that solifenacin exerts an inhibitory effect on afferent pathways both systemically and locally, and its effect contributes to the inhibition of bladder overactivity, at least in part.

It has been known that afferent pathways from urinary bladder are activated by various neurotransmitters including ACh, ATP, prostaglandins, and nerve growth factors. Recently, inhibition of ATP release from urothelium is considered to be involved in the suppression of afferent pathways. Non-neuronal ACh release from urothelium is induced by stretching of the human bladder, and the stimulation of M_3 and M_3 receptors on urothelium induces non-neuronal ATP release (4). Solifenacin inhibited this non-neuronal ATP release by blocking the M_3 receptors on the urothelium, resulting in the inhibition of afferent pathways (4). Especially, solifenacin showed the inhibitory effect at lower concentrations compared with oxybutynin, propiverine, and tolterodine. On the other hand, bladder instillation of acetic acid is known to induce increases in urinary ATP level and decreases in bladder capacity in rats. In this rat model, solifenacin has been reported to inhibit both the increase in urinary ATP levels and decrease in bladder capacity (22). Solifenacin therefore suppresses afferent pathways partly by inhibition of non-neuronal ATP release from urothelium.

3. Discussion

It has been demonstrated that solifenacin has high affinity for the M_3 receptor, which modulates bladder contraction, and increases bladder capacity and voided
volume in a rat model of OAB. Solifenacin has been confirmed to show greater selectivity for urinary bladder over salivary gland than other antimuscarinic agents. In addition, solifenacin has inhibitory effects on afferent pathways from urinary bladder via the inhibition of nonneuronal ATP release, partly related to a local effect by the excreted urine. These inhibitory effects of solifenacin on excess bladder contraction and afferent activation are considered to confirm its clinical efficacy for OAB symptoms.

Recently, several clinical studies with a focus on urgency-related endpoints, the principal OAB symptom, have been reported. In a double-blind, placebo-controlled trial, the efficacy and tolerability of solifenacin treatment for OAB was assessed (23, 24). Patients were randomized to once-daily solifenacin (5/10 mg) or placebo for 12 (23) or 16 (24) weeks. The mean number of urgency episodes per 24 h, the primary endpoint, decreased by 3.91 (from 6.15 to 2.24) with solifenacin and by 2.73 (from 6.03 to 3.30) with placebo ($P < 0.0001$) (23). Solifenacin was also significantly more effective than placebo in reducing the mean number of episodes of severe urgency from baseline to endpoint ($−2.6 \text{ vs. } −1.8$, $P < 0.001$) (24). Median warning time (defined as the time from first sensation of urgency to voiding), a secondary endpoint, increased 31.5 s (baseline, 67.8 s) with solifenacin, significantly longer ($P = 0.008$) than the median increase of 12 s (baseline, 65.0 s) observed with placebo (23). This prolongation of warning time was reflected by significant decreases in incontinence episodes compared with placebo. Subjective endpoints by patients (urgency bother, patient perception of bladder condition, treatment satisfaction) were also significantly improved with solifenacin compared with placebo (24). In addition, solifenacin significantly improved other OAB symptoms, such as micturition frequency and incontinence episodes compared with placebo in these clinical trials. The most common adverse effects with solifenacin were dry mouth, constipation and blurred vision of mild or moderate severity. The discontinuation rate owing to adverse effects was 3.6% – 6.5% with solifenacin and 2.4% – 4.6% with placebo (23, 24).

As described above, solifenacin showed statistically significant efficacy by both subjective and objective evaluation compared with placebo, with low incidence of adverse effects. The direct evaluation of urgency in preclinical studies is difficult. However, given that solifenacin has been demonstrated to suppress the afferent pathways in various preclinical studies, it is considered to have the effect of improving urgency.

4. Conclusions

Solifenacin has been confirmed to be a useful drug that shows statistically significant efficacy against all symptoms of OAB, including urgency, with good tolerability. This profile is based on the high bladder selectivity and suppression of afferent pathways with solifenacin.

Acknowledgments

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References

Effect of Solifenacin on Urgency Episodes