Phenotype pharmacology of lower urinary tract $\alpha_1$-adrenoceptors

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$\alpha_1$-adrenoceptors are involved in numerous physiological functions, including micturition. However, the pharmacological profile of the $\alpha_1$-adrenoceptor subtypes remains controversial. Here, we review the literature regarding $\alpha_1$-adrenoceptors in the lower urinary tract from the standpoint of phenotype pharmacology. Among three $\alpha_1$-adrenoceptor subtypes ($\alpha_{1a}$, $\alpha_{1b}$ and $\alpha_{1c}$), $\alpha_{1c}$-adrenoceptor mRNA is the most abundantly transcribed in the prostate, urethra and bladder neck of many species, including humans. In prostate homogenates or membrane preparations, $\alpha_{1c}$-adrenoceptors with high affinity for prazosin have been detected as radioligand binding sites. Functional $\alpha_1$-adrenoceptors in the prostate, urethra and bladder neck have low affinity for prazosin, suggesting the presence of an atypical $\alpha_1$-adrenoceptor phenotype (designated as $\alpha_{1c}$).

The $\alpha_{1c}$-adrenoceptor occurs as a distinct binding entity from the $\alpha_{1a}$-adrenoceptor in intact segments of various tissues including prostate. Both the $\alpha_{1a}$- and $\alpha_{1c}$-adrenoceptors are specifically absent from Adra1A ($\alpha_{1a}$) gene-knockout mice. Transfection of $\alpha_{1a}$-adrenoceptor cDNA predominantly expresses $\alpha_{1a}$-phenotype in several cultured cell lines. However, in CHO cells, such transfection expresses $\alpha_{1a}$- and $\alpha_{1c}$-phenotypes. Under intact cell conditions, the $\alpha_{1c}$-phenotype is predominant when co-expressed with the receptor interacting protein, CRELD1a. In summary, recent pharmacological studies reveal that two distinct $\alpha_1$-adrenoceptor phenotypes ($\alpha_{1a}$ and $\alpha_{1c}$) originate from a single Adra1A ($\alpha_{1a}$-adrenoceptor) gene, but adrenergic contractions in the lower urinary tract are predominantly mediated via the $\alpha_{1c}$-adrenoceptor. From the standpoint of phenotype pharmacology, it is likely that phenotype-based subtypes such as the $\alpha_{1c}$-adrenoceptor will become new targets for drug development and pharmacotherapy.
maintain continence. There is good pharmacological evidence supporting the view that noradrenaline-mediated contraction of the urethral smooth muscle has an important role (Andersson and Wein, 2004).

Among impairments in urine storage, stress urinary incontinence (SUI) is recognized as one of the most frequently occurring conditions. Deficient urethral or bladder neck closure may result in this condition. However, drug treatments for SUI are scarce, at present (Andersson and Wein, 2004). The density of noradrenergic nerves increases markedly towards the bladder neck and urethra (Gosling et al., 1999).

1-Adrenoceptors play important roles in both urethral and bladder neck contraction, and may be related to SUI (Andersson and Wein, 2004).

During the voiding phase, prostatic smooth muscle tone contributes to outlet resistance regulation. Benign prostatic hyperplasia (BPH) is a common enlargement of the prostate gland that may lead to bladder outlet obstruction, and lower urinary tract symptoms. BPH is currently recognized as a target for pharmacotherapy utilizing α1-adrenoceptor antagonists. In BPH patients, enlargement of the prostate increases bladder outlet resistance and thereby impedes physiological voiding. α1-Adrenoceptor antagonists are believed to inhibit contraction of the prostate and urethra, and as a result, α1-adrenoceptor antagonists such as tamsulosin, alfuzosin and silodosin effectively reduce resistance to urinary flow and are now clinically used in BPH patients (Lefevre-Borg et al., 1993; Cooper et al., 1999; Ruffolo and Hieble, 1999; Takeda et al., 1999; Chapple, 2001; Andersson, 2002; Michel and Vrydag, 2006).

The functional roles of α1-adrenoceptors have been highlighted through the study of their roles in lower urinary tract physiology. These are supported by numerous studies including quantification of mRNAs, anatomical localization of mRNAs, or of receptors demonstrated by ligand-binding studies (Table 1). On the other hand, functional studies have shown discrepancies between the native α1-adrenoceptors found in the lower urinary tract (so-called α1L-adrenoceptor) and the classical α1-adrenoceptors (α1A, α1B and α1D; receptor nomenclature follows Alexander et al., 2011) (Table 2). Subsequent studies revealed the origin of these unique α1-adrenoceptors in the lower urinary tract (Ford et al., 1997; Gray et al., 2008; Muramatsu et al., 2008; Nishimune et al., 2010b). In this review, we will introduce recent progress in the study of α1-adrenoceptors in the lower urinary tract as an example of the importance of phenotype pharmacology (Kenakin, 2003; Muramatsu et al., 2005; 2008; Nelson and Challiss, 2007; Su et al., 2008).
Table 1

α₁-Adrenoceptor subtypes in lower urinary tract

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Species</th>
<th>mRNA</th>
<th>Binding</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Rat</td>
<td>α₁a, 1,2</td>
<td>α₁a, 12</td>
<td>α₁a, 12,18,19</td>
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<tr>
<td></td>
<td></td>
<td>α₁b, 1, 4</td>
<td>α₁b, 15</td>
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<td></td>
<td></td>
<td>α₁L, 3, 5</td>
<td>α₁L, 13</td>
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<tr>
<td>Rabbit</td>
<td></td>
<td>α₁a, 6</td>
<td>α₁a, 14</td>
<td>α₁a, 20–22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α₁b, 8–11</td>
<td>α₁b, 14</td>
<td>α₁b, 14-23-25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α₁L, 16</td>
<td>α₁L, 17</td>
<td>α₁L, 15, 17-30</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td>α₁a &gt; α₁b &gt; α₁L</td>
<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α₁b &gt; α₁L</td>
<td>α₁b, 17</td>
<td>α₁b, 15-17-30</td>
</tr>
<tr>
<td>Urethra</td>
<td>Rat</td>
<td>α₁a &gt; α₁b &gt; α₁L</td>
<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td></td>
<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
</tr>
<tr>
<td></td>
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<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
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<tr>
<td>Bladder neck</td>
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<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td></td>
<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
</tr>
<tr>
<td></td>
<td>Human</td>
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<td>α₁a, 15</td>
<td>α₁a, 15-18,19,26-29</td>
</tr>
</tbody>
</table>

mRNA: subtypes identified from RT-PCR studies or RNase protection assays.
Binding: subtypes detected by radioligand binding assay with tissue homogenates or membrane preparations, but in References 14 and 17, tissue segments were also used in binding assay.
Function: data obtained from bioassay where the contractile responses to noradrenaline or other α₁-agonists were examined. According to the standard nomenclature (Alexander et al., 2011), the term α₁x is used to refer to receptor subtype. In this review, we will use the term only for receptor phenotype in order to focus on phenotypic variation (α₁a, or α₁L) arising from the same gene (Adra1A). To refer to receptor polypeptide, we instead use the term α₁x.

The superscripted numbers refer to the relevant reference and are shown here in short form; the full form is provided in the usual list of references below.


Table 2

α₁-Adrenoceptor subtypes and their pharmacological characterization

<table>
<thead>
<tr>
<th>Gene</th>
<th>Receptor polypeptide</th>
<th>Phenotype</th>
<th>Affinity (mean pK₉)</th>
<th>Prazosin</th>
<th>Silodosin</th>
<th>Tamsulosin</th>
<th>RS-17053</th>
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</thead>
<tbody>
<tr>
<td>ADRA1A</td>
<td>α₁a</td>
<td>α₁a</td>
<td>9.6</td>
<td>9.8</td>
<td>10.0</td>
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<tr>
<td></td>
<td>α₁L</td>
<td>α₁L</td>
<td>8.0</td>
<td>9.8</td>
<td>10.0</td>
<td>6.3</td>
<td></td>
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<tr>
<td>ADRA1B</td>
<td>α₁b</td>
<td>α₁b</td>
<td>10.2</td>
<td>8.0</td>
<td>9.3</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α₁L</td>
<td>α₁L</td>
<td>10.0</td>
<td>8.4</td>
<td>9.9</td>
<td>7.8</td>
<td></td>
</tr>
</tbody>
</table>

Affinity values are from Morishima et al. (2007).

2006). Interestingly, however, the α₁a-adrenoceptor mRNA detected at the tissue level disappears in cultures of human prostatic smooth muscle cells, in contrast to the consistent expression of α₁α- and α₁L-adrenoceptor mRNAs (Boesch et al., 1999). The relative expression of α₁a-adrenoceptor mRNA in the lower urinary tract of humans has also been examined by in situ hybridization studies. In the human prostate, α₁a-adrenoceptor mRNA was mainly detected in the stroma,
including smooth muscle cells, but not in the glandular epithelium (Walden et al., 1999).

Data regarding the expression of α₁-adrenoceptor mRNA in the human bladder are inconsistent, but it appears that the expression of α₁-adrenoceptor mRNA is extremely low in the bladder (Malloy et al., 1998; Nomiyama and Yamaguchi, 2003). In the human detrusor, β (mainly β₃) adrenoceptors are dominant over α-adrenoceptors, based on the fact that the normal response to noradrenaline is relaxation rather than contraction (Andersson, 1993). Therefore, we can conclude that the functional significance of α-adrenoceptors in the detrusor contraction may be marginal or non-existent (Fig. 1). On the other hand, the density of noradrenergic nerves increases markedly towards the bladder neck, where the smooth muscle receives a dense noradrenergic nerve supply (Gosling et al., 1999). In the human bladder, the predominant expression of α₁-adrenoceptor mRNA in the dome, trigone and base has also been reported (Walden et al., 1997).

Thus, the mRNA data in human urinary tract indicate that the α₁-adrenoceptor polypeptide is a potential target for pharmacotherapy in patients with BPH and SUI.

α₁-Adrenoceptor pharmacological anomalies in the lower urinary tract

The classical α₁-adrenoceptors (α₁A, α₁B and α₁D) show high affinity for prazosin (pKᵢ or pKB > 9) in most binding and functional studies (Lomasney et al., 1991; Hieble et al., 1995; Ford et al., 1996; Thouroux et al., 1996; Taniguchi et al., 1999; Suzuki et al., 2000; Israilova et al., 2004) (Table 2). However, the functional α₁-adrenoceptors identified in the lower urinary tract are known to be relatively resistant to prazosin (Muramatsu et al., 2009) (pKᵢ ≈ 8) (Table 1). Thus, this pharmacological anomaly, despite the predominance of α₁-adrenoceptor mRNA, caused confusion about the α₁-adrenoceptor subtypes in the lower urinary tract. Because different affinities for antagonists have traditionally been regarded as characteristic pharmacological criteria for defining novel receptors (Kenakin, 1995; Rang, 2006), the anomalous α₁-adrenoceptor showing low affinity for prazosin suggests the existence of a distinctive subtype (or phenotype).

Pharmacological heterogeneity of α₁-adrenoceptors was originally reported by Drew (1985), who first noted a wide variation in the functional affinities for yohimbine and prazosin. This evidence was confirmed in experiments with isolated blood vessels by Flavahan and Vanhoutte (1986), and was subsequently extended by many pharmacologists and in many tissues including the lower urinary tract (Muramatsu et al., 1990; 1991; Ford et al., 1996; Testa et al., 1997; Stäm et al., 1999; Argyle and McGrath, 2000). In this subclassification, the classical α₁A, α₁F and α₁D-adrenoceptors are included in the α₁β group, and the anomalous α₁-adrenoceptor showing low affinity for prazosin in the lower urinary tract has been reported as the α₁L-adrenoceptor (Muramatsu et al., 1991; 1995; Ford et al., 1996; Langer, 1999; Nishimune et al., 2010a). Antagonistic potencies against noradrenaline-induced contractions in rat, rabbit and human prostate are low for prazosin (pKᵢ = −8) and α₁L-antagonists (5-methylurapidil, WB4101, RS-17053), but are high for silodosin and tamsulosin (Hiraoka et al., 1995; 1999; Ford et al., 1996; Leonardi et al., 1997; Testa et al., 1997; Van der Graaf et al., 1997; Morishima et al., 2007; Su et al., 2008). In contrast to this nomenclature, α₁-adrenoceptors in the lower urinary tract have been also named as α₁-adrenoceptors in many reports (Table 1). Therefore, there has been confusion in defining the functional α₁-adrenoceptor in the lower urinary tract (Table 1), which may in part depend on distinct subclassifications (α₁A, α₁L vs. α₁L, α₁B, α₁D).

α₁-adrenoceptor can also be detected at the mRNA and protein levels in urogenital tissues (Yablonsky et al., 1986; Michel and Vrydag, 2006). Therefore, the anomalous characteristics of adrenergic contractions in the lower urinary tract may be associated with the α₁-adrenoceptor. In fact, clonidine (α₂-agonist) can produce a significant contraction in the female rabbit urethra (Larsson et al., 1986). However, clonidine is inactive in the isolated female human urethra, while noradrenaline produces contractions through sites with low affinity for prazosin (Taki et al., 1999). These results show that the α₁-adrenoceptor is not significantly involved in the anomalous contraction in the human urethra (Ruffolo and Hieble, 1999), although there may be relevant species differences in this adrenoceptor.

Identification of α₁-adrenoceptors by radioligand binding assay

Because reliable subtype-specific α₁-adrenoceptor antibodies were recently reported to be unavailable (Jensen et al., 2009), investigation of α₁-adrenoceptors at the protein level are herein summarized from radioligand-binding experiments.

Binding assay with membrane homogenates

Specific binding of [³H]-prazosin, [¹²⁵I]-HEAT, [³H]-tamsulosin and [³H]-silodosin to α₁-adrenoceptors in membrane preparations of the lower urinary tract has been detected, with the density of binding in the prostate > urethra > bladder. In the rat, rabbit and human prostate, the most abundant α₁-adrenoceptor is the α₁L-subtype, which has been identified as having high affinity for prazosin, tamsulosin, silodosin and other α₁L-selective antagonists (5-methylurapidil and RS-17053) (Tables 1 and 2). Thus, low-affinity sites for prazosin (α₁L-adrenoceptors) are not detected in the membrane preparations of lower urinary tract tissues and at subnanomolar concentrations of [³H]-prazosin. The high abundance of the binding sites showing α₁L-adrenoceptor profile in the lower urinary tract is in agreement with the mRNA expression data mentioned above.

Three α₁-adrenoceptor cDNAs (including splice variants of α₁L-adrenoceptors) were transfected in several cell lines (CHO cells, COS-7 cells, HEK 293 cells, HeLa cells) and the pharmacological binding characteristics in the membrane preparations were compared with those in native tissues. The three recombinant α₁-adrenoceptors showed high (subnanomolar) affinity for prazosin (Table 2). The cloned α₁L-
adrenoceptor and its splice variants showed the same pharmacological profile as that recognized in the membrane preparations of lower urinary tract (Lomasney et al., 1991; Theroux et al., 1996; Piao et al., 2000; Suzuki et al., 2000; Ramsay et al., 2004).

**Binding assay with whole cells and intact tissues**

Most radioligand-binding studies conducted to date have involved homogenates or membrane preparations of tissues or cells as a source of receptors. Because tissue/cell homogenization physically disturbs the receptor microenvironment, it may cause changes in some of the pharmacological characteristics of the receptor. Therefore, in order to retain the natural/native receptor conformation by minimizing physical agitation, whole cells or intact tissue segments must be used in binding assays.

Ford and co-workers reported that the pharmacological characteristics of the recombinant \( \alpha_{1A} \)-adrenoceptor can vary substantially depending upon assay conditions (Ford et al., 1997; Daniels et al., 1999). In CHO cells expressing the recombinant \( \alpha_{1A} \)-adrenoceptor, prazosin and RS-17053 (\( \alpha_{1A} \)-selective antagonist) show substantially lower potency against functional responses (phosphatidyl inositol turnover and calcium influx) in intact cells than inhibition of radioligand binding to \( \alpha_{1A} \)-adrenoceptors in membrane homogenates. Furthermore, the \( K_i \) values for prazosin and RS-17053 as competitive inhibitors of \([H]-prazosin binding to \( \alpha_{1A} \)-adrenoceptors in these CHO cells are dependent on assay conditions, with lower affinity observed when binding is conducted under more physiological conditions (culture medium, intact cells, 37°C) than under conditions commonly employed for radioligand binding assays (artificial buffer, membrane homogenates, 20°C). These observations have led to the proposal that the \( \alpha_{1A} \)-adrenoceptor may not represent an independent molecular entity, but rather may be an ‘affinity state’ of the \( \alpha_{1A} \)-adrenoceptor that is predominant in lower urinary tract.

Recently, a tissue segment binding method was developed and applied to numerous tissues (Tanaka et al., 2004; Muramatsu et al., 2005). In this method, tissue segments are incubated (without homogenization) in a nutrient medium such as Krebs solution during the course of ligand binding. To identify the \( \alpha_{1A} \)-adrenoceptors having low affinity for prazosin, \([H]-silodosin was used instead of \([H]-prazosin, because \([H]-prazosin at subnanomolar concentrations cannot bind sufficiently to \( \alpha_{1A} \)-adrenoceptors (Su et al., 2008; Muramatsu et al., 2009). Silodosin and its tritiated radioligand are known to be of equally high affinity for both the \( \alpha_{1A} \) and \( \alpha_{1L} \)-adrenoceptors (Murata et al., 1999; Su et al., 2008) (Table 2).

In segments of human, mouse and rabbit prostate, the binding of \([H]-silodosin was biphasically displaced by prazosin, indicating the coexistence of high and low-affinity sites for prazosin, which correspond to \( \alpha_{1A} \) and \( \alpha_{1L} \)-adrenoceptors (Morishima et al., 2007; Muramatsu et al., 2008; Su et al., 2008). This result is very different from the results obtained in homogenates, in which a single high-affinity site for prazosin (\( \alpha_{1L} \)-adrenoceptor) was detected. The low-affinity site for prazosin in the prostate segments also showed low affinity for some \( \alpha_{1A} \)-selective antagonists (RS-17053, 5-methylurapidil), but tamsulosin (which has high affinity for \( \alpha_{1A} \)-, \( \alpha_{1\omega} \) and \( \alpha_{1L} \)-subtypes) did not discriminate either the high- or low-affinity sites for prazosin. Similar results were obtained in studies of other tissues in which the \( \alpha_{1L} \)-adrenoceptor was identified as a functional receptor (Hiraizumi-Hiraoka et al., 2004; Morishima et al., 2008; Muramatsu et al., 2008; 2009). From these observations, it was suggested that \( \alpha_{1A} \)-adrenoceptors (or \( \alpha_{1\omega} \)-phenotype) coexist with \( \alpha_{1L} \)-adrenoceptors (or \( \alpha_{1L} \)-phenotype) as pharmacologically distinct entities under intact segment conditions, whereas the pharmacological profile of \( \alpha_{1A} \)-adrenoceptors converts to the \( \alpha_{1L} \)-phenotype upon homogenization.

More recently, this conclusion was again confirmed in a recombinant system (Nishimune et al., 2010b). In the CHO cell line, transfection of \( \alpha_{1A} \)-adrenoceptor cDNA predominantly expresses \( \alpha_{1A} \)-adrenoceptor phenotype, with an extremely minor proportion of \( \alpha_{1L} \)-adrenoceptor (less than 10% of total \( \alpha_{1} \)-adrenoceptor). However, persistent overexpression of the protein, cysteine-rich epidermal growth factor-like domain 1a (CRELD1a), which was found as a potential \( \alpha_{1A} \)-adrenoceptor-interacting protein candidate) strongly reduced the population of \( \alpha_{1L} \)-adrenoceptor phenotype in CHO cells (Nishimune et al., 2010b). Although mechanisms underlying the interactions between generation of CRELD1a and \( \alpha_{1A} \)-adrenoceptors and \( \alpha_{1L} \)-adrenoceptors remain unclear, two distinct \( \alpha_{1L} \)-adrenoceptor-dominant and \( \alpha_{1A} \)-adrenoceptor-dominant) CHO cell lines were eventually established. Under whole-cell conditions, in contrast to the \( \alpha_{1A} \)-adrenoceptor, pharmacological and functional properties of the established \( \alpha_{1L} \)-adrenoceptor show low affinity for prazosin and other \( \alpha_{1A} \)-adrenoceptor agonists (5-methylurapidil, RS-17053), and the agonist and antagonist pharmacology is consistent with the profile of the \( \alpha_{1L} \)-adrenoceptor identified in the lower urinary tract. Therefore, from these lines of evidence, it may be now concluded that the \( \alpha_{1L} \)-adrenoceptor is one of the \( \alpha_{1} \)-adrenoceptor gene products and occurs as an entity distinct from the \( \alpha_{1A} \)-adrenoceptor phenotype under conditions when the tissue/cell is kept intact. This conclusion would also explain why \( \alpha_{1A} \)-adrenoceptors could not be detected after homogenization but are easily recognized in functional bioassay studies with intact tissue strips (Muramatsu et al., 2009).

**Identification of the gene encoding \( \alpha_{1L} \)-adrenoceptor**

Despite extensive searches at early stages after the proposal of the \( \alpha_{1L} \)-adrenoceptor and the subsequent completion of the human genome sequencing project, a distinct gene for the proposed \( \alpha_{1L} \)-adrenoceptor has not been identified. Rather, as described above, a close relationship between \( \alpha_{1A} \)-adrenoceptor and \( \alpha_{1L} \)-adrenoceptor has been considered (Ford et al., 1997; Hiraizumi-Hiraoka et al., 2004; Morishima et al., 2008).

In order to explore this possible link between \( \alpha_{1A} \) and \( \alpha_{1L} \)-adrenoceptors, we analysed \textit{in vivo} phenotypes of mice having disrupted alleles of the classical \( \alpha_{1} \)-adrenoceptors (\( \alpha_{1A} \), \( \alpha_{1\omega} \) and \( \alpha_{1\eta} \)) (Muramatsu et al., 2008). The integrity of the \( \alpha_{1L} \)-adrenoceptors were confirmed both in terms of ligand...
binding properties and contractile function in the Adra1B\(^{-/-}\) (\(\alpha_{1b}^{\text{re}}\)) and Adra1D\(^{-/-}\) (\(\alpha_{1d}^{\text{re}}\)) mice as well as in the wild-type mice. In contrast, both \(\alpha_{1a}\)- and \(\alpha_{1L}\)-adrenoceptors were completely absent from the Adra1A\(^{-/-}\) (\(\alpha_{1a}^{\text{re}}\)) mice. These results unequivocally demonstrate that both \(\alpha_{1a}\)-adrenoceptors and \(\alpha_{1L}\)-adrenoceptors are derived from the same Adra1A (\(\alpha_{1a}\)) gene (Gray et al., 2008; Muramatsu et al., 2008) (Table 2).

Observation of \(\alpha_{1L}\)-adrenoceptor distribution by fluorescent probe

Alexa Fluor 488 dye conjugated with silodosin (Alexa-488-silodosin) was recently introduced as a fluorescent probe (Morishima et al., 2010). Alexa-488-silodosin retains the high affinity and selectivity for \(\alpha_{1a}\) and \(\alpha_{1L}\)-adrenoceptors as shown by unlabelled silodosin. Histochemical experiments with this fluorescent probe clearly showed that Alexa-488-silodosin binds to the smooth muscle but not the glandular tissue in the human prostate, and that the binding is resistant to low concentrations of prazosin. These results are in good agreement with in situ hybridization data showing selective expression of \(\alpha_{1L}\)-adrenoceptor mRNA in the stroma of the human prostate (Walden et al., 1999). As the Alexa-488-silodosin can specifically label \(\alpha_{1L}\)-adrenoceptors, particularly by co-incubation with low concentrations of prazosin (to mask the \(\alpha_{1a}\)-adrenoceptor), this novel molecular probe provides a versatile tool to study \(\alpha_{1L}\)-adrenoceptor histochemically (Morishima et al., 2010).

Perspective

As mentioned above, recent progress in this field clearly demonstrates that two distinct \(\alpha_{1}\)-adrenoceptor phenotypes (\(\alpha_{1A}\) and \(\alpha_{1L}\)) originate from a single \(\alpha_{1}\)-adrenoceptor gene and coexist in some tissues. However, adrenergic contraction in the lower urinary tract is predominantly mediated through \(\alpha_{1L}\), but not \(\alpha_{1A}\)-adrenoceptors (Fig. 1). In general, the affinity values (pKi or pKd) for prazosin for \(\alpha_{1A}\)-adrenoceptors are around 8, but recent studies reveal a further variation in prazosin affinity (pKi or pKd = 6.3–8.5) at various \(\alpha_{1}\)-adrenoceptors in many tissues and species (Muramatsu et al., 2009). This is reminiscent of the original question on \(\alpha_{1}\)-adrenoceptors (Drew, 1985), suggesting further heterogeneity in \(\alpha_{1L}\)-adrenoceptor pharmacology. At present, the mechanisms underlying the expression of \(\alpha_{1L}\)-adrenoceptor phenotype and its functional predominance in several tissues remain unknown. However, it is likely that the expression of divergent \(\alpha_{1}\)-adrenoceptor phenotypes is strongly dependent on any modification of the tissues of various species, rather than a simple variation of the \(\alpha_{1}\)-adrenoceptor protein or additional subtypes (Muramatsu et al., 2009; Nishimune et al., 2010a).

Recently, ample evidence has been accumulating suggesting that antagonist affinity is not necessarily constant at a given receptor expressed in different tissues/cells and examined under different assay conditions (Kenakin, 2003; Baker and Hill, 2007; Nelson and Challiss, 2007; Muramatsu et al., 2008). The \(\alpha_{1L}\)-adrenoceptor exemplifies this type of variable affinity, as after homogenization, the phenotype changed from \(\alpha_{1a}\) into \(\alpha_{1l}\). It is likely that tissue integrity is an important factor to determine receptor properties (Su et al., 2008; Muramatsu et al., 2009). Therefore, we may have to re-evaluate pharmacodynamic and pharmacokinetic effects of currently used drugs, and to reconstruct drug development strategies. Now, \(\alpha_{1}\)-antagonists, such as tamsulosin, silodosin, alfuzosin, are clinically used in BPH patients. According to the evidence mentioned above, these antagonists appear to act mainly on functional \(\alpha_{1A}\)-adrenoceptors in the lower urinary tract, but are not specific for the \(\alpha_{1L}\)-adrenoceptor. The \(\alpha_{1L}\)-adrenoceptors in the female urethra may be a new target in therapy for SUI. For this purpose, two \(\alpha_{1}\)-adrenoceptor agonists (NS-49 and Ro 115-1240) have been developed. However, these compounds are full agonists of the \(\alpha_{1A}\)-adrenoceptor or partial agonists of the \(\alpha_{1L}\)-adrenoceptor (Obika et al., 1995; Blue et al., 2004; Musselman et al., 2004). Thus, more selective or specific drugs against \(\alpha_{1L}\)-adrenoceptors may lead to improved uroselectivity.

Conclusion

Since the successful cloning of most receptors, it has become possible to elucidate numerous physiological responses by genome-based subtype (genotypes). However, there are still some unique phenotypes showing distinct pharmacology in native tissues. The \(\alpha_{1L}\)-adrenoceptor is representative of this group, and originates from the \(\alpha_{1L}\)-adrenoceptor gene together with the \(\alpha_{1C}\)-adrenoceptor phenotype. In this review, we propose that different phenotypes are expressed from a single gene in native tissues (‘one gene-multiple phenotypes theory’), which may explain the long controversy regarding some putative receptors, such as \(\alpha_{1L}\)-adrenoceptor in the lower urinary tract, and further highlights phenotype-dependent pharmacology (‘phenotype pharmacology’).

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Conflict of interest

The authors declare no competing financial interests.

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