Brief Report

Selectivity and Maximum Response of Vibegron and Mirabegron for \( \beta_3 \)-Adrenergic Receptors

Benjamin M. Brucker, MD, Jennifer King, PharmD, Paul N. Mudd Jr, PharmD, MBA, Kimberly McHale, PhD

1 Departments of Urology and Obstetrics and Gynecology, NYU Langone Health, New York, New York
2 Urology Sciences, Irvine, California
3 Currently at: Cytheron Therapeutics, Boston, Massachusetts
4 Currently at: Priorvant Therapeutics, Durham, North Carolina
5 Dermavant Sciences, Morrisville, North Carolina

ABSTRACT

Background: The \( \beta_3 \)-adrenergic agonists vibegron and mirabegron have shown favorable safety profiles and efficacy for the treatment of overactive bladder. However, \( \beta \)-adrenergic receptors are also found outside the bladder, which could lead to off-target activity.

Objective: This study assessed the selectivity of vibegron and mirabegron for \( \beta \)-adrenergic receptors and the maximal effect and potency for \( \beta_3 \)-adrenergic receptors.

Methods: Functional cellular assays were performed using Chinese hamster ovary-K1 cells expressing \( \beta_1 \)-, Chinese hamster ovary cells expressing \( \beta_2 \)-, and human embryonic kidney 293 cells expressing \( \beta_3 \)-adrenergic receptors. Cells were incubated with vibegron, mirabegron, or control (\( \beta_1 \) and \( \beta_3 \), isoproterenol; \( \beta_2 \), procaterol). Responses were quantified using homogeneous time-resolved fluorescence of cyclic adenosine monophosphate and were normalized to the respective control. Half-maximal effective concentration and maximum response values were determined by nonlinear least-squares regression analysis.

Results: Activation of \( \beta_3 \)-adrenergic receptors with vibegron or mirabegron resulted in concentration-dependent \( \beta_3 \)-adrenergic receptor responses. Mean (SEM) half-maximal effective concentration values at \( \beta_3 \)-adrenergic receptors were 2.13 (0.25) nM for vibegron and 10.0 (0.56) nM for mirabegron. At a concentration of 10 \( \mu \)M, \( \beta_1 \)-adrenergic activity relative to isoproterenol was 104% for vibegron and 88% for mirabegron. Maximum response at \( \beta_3 \)-adrenergic receptors was 99.2% for vibegron and 80.4% for mirabegron. \( \beta_1 \)-adrenergic activity was 0% and 3% for vibegron and mirabegron, respectively; \( \beta_2 \)-adrenergic activity was 2% and 15%, respectively.

Conclusions: Vibegron showed no measurable \( \beta_1 \) and low \( \beta_2 \) activity compared with mirabegron, which showed low \( \beta_1 \) and some \( \beta_2 \) activity. Both showed considerable selectivity at \( \beta_3 \)-adrenergic receptors; however, vibegron demonstrated near-exclusive \( \beta_3 \) activity and a higher maximum \( \beta_3 \) response.

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Introduction

Overactive bladder (OAB) is highly prevalent in adults and is characterized by symptoms such as urgency with or without urge urinary incontinence. First-line treatment for OAB includes behavioral therapy with or without pharmacotherapy; second-line treatment includes oral anticholinergics and \( \beta_3 \)-adrenergic receptor agonists. However, treatment with anticholinergic agents is associated with bothersome side effects such as dry mouth and constipation that can limit treatment persistence, as well as an increased risk of falls and potential for impaired cognitive function. The \( \beta_3 \)-adrenergic receptor agonists are a class of treatment for OAB that minimize several of the adverse effects associated with anticholinergic use. Vibegron and mirabegron are \( \beta_3 \)-adrenergic receptor agonists that are currently approved in the United States, Europe (mirabegron only), and Japan for the treatment of OAB.

The \( \beta \)-adrenergic receptors are G protein-coupled receptors that vary in structure, expression, and function. The human \( \beta_3 \)-adrenergic receptor shares approximately 50% of its sequence
with the $\beta_1$- and $\beta_2$-receptors.\textsuperscript{13,14} Compared with $\beta_2$-, the $\beta_3$-adrenergic receptor lacks C-terminal phosphorylation sites that in $\beta_2$-adrenergic receptors are associated with agonist-induced desensitization.\textsuperscript{15} In the bladder and detrusor muscles, $\beta_3$-adrenergic receptors account for 94% to 97% of $\beta$-adrenergic receptor mRNA.\textsuperscript{16,17} The primary function of $\beta_3$-adrenergic receptors in the bladder is to aid in detrusor smooth muscle relaxation during the filling stage of the micturition cycle.\textsuperscript{17,18} In addition to the bladder and detrusor muscle, $\beta$-adrenergic receptors are expressed on cardiovascular tissue (reviewed in Wachter et al\textsuperscript{19}), inviting concerns about potential off-target effects associated with the use of $\beta$-adrenergic agonists if they are not highly selective for a given receptor subtype. Beyond selectivity, potency at $\beta_3$-adrenergic receptors may influence efficacy.

Both vibegron and mirabegron act on the $\beta_3$-adrenergic receptor; however, there are innate differences associated with their unique pharmacologies. Because earlier generations of $\beta_3$-adrenergic agonists were associated with the buildup of toxic metabolites and with off-target effects, the structure of vibegron was carefully chosen and intentionally designed to improve upon $\beta_3$-adrenergic agonists that had failed preclinically.\textsuperscript{20,21} Mirabegron has been shown to stimulate $\beta_1$-adrenergic receptors at supratherapeutic doses, leading to increases in contractile force in the atrium.\textsuperscript{11,22}

Additional differences between vibegron and mirabegron include dose and titration requirements. In the Phase III EMPOWUR and EMPOWUR extension studies, once-daily vibegron 75 mg showed safety and efficacy for the treatment of OAB\textsuperscript{10,23} at a single dose strength. Steady state concentrations of vibegron are reached within 7 days of once-daily dosing, and the effective half-life is 30.8 hours. For the treatment of OAB, the recommended 25-mg starting dose of mirabegron has an onset of action of up to 8 weeks,\textsuperscript{10} and therefore dose escalation to 50 mg may be required. Mirabegron 50 mg has been shown to be effective within 4 weeks.\textsuperscript{10,24}

The selectivity of vibegron and mirabegron for $\beta$-adrenergic receptors has not been tested in a head-to-head fashion. The aim of this study was to assess and compare the selectivity of vibegron and mirabegron for each $\beta$-adrenergic receptor subtype, as well as the maximal effect and potency for $\beta_3$-adrenergic receptors.

**Methods**

**Cells and cell culture**

Chinese hamster ovary (CHO)-K1, CHO, and human embryonic kidney (HEK) 293 cells stably expressing human $\beta_1$-, $\beta_2$-, or $\beta_3$-adrenergic receptors, respectively, and HEK293 and CHO-K1 cells expressing human $\alpha_{1D}$- and $\alpha_{2B}$-adrenergic receptors, respectively, were provided by Eurofins Panlabs (Taipei, Taiwan). Cell lines were cultured at 37°C with 5% carbon dioxide. CHO-K1 and CHO cells were cultured in Dulbecco’s modified Eagle’s medium/Ham’s F12 supplemented with 2 mM L-glutamine and 10% (v/v) heat-inactivated fetal calf serum. HEK293 cells were cultured in Eagle’s minimal essential medium and Earle’s balanced salt solution supplemented with 1% (v/v) minimal essential medium nonessential amino acids, 2 mM L-glutamine, and 10% (v/v) heat-inactivated fetal calf serum.

**Selectivity and potency assays**

Cells were plated at a density of $2.5 \times 10^5$ cells/mL for $\beta$-receptor selectivity and potency, assays were performed in an incubation buffer consisting of Hank’s balanced salt solution containing 5 mM HEPES, 0.1% (w/v) bovine serum albumin, and 100 μM 3-isobutyl-1-methylxanthine (a phosphodiesterase inhibitor), pH 7.4. For $\alpha$-receptor selectivity, assays were performed in an incubation buffer consisting of 50 mM Tris-HCl, pH 7.4; for $\alpha_{2B}$ assays, incubation buffer was supplemented with 1 mM EDTA, 12.5 mM magnesium chloride, and 0.2% (w/v) bovine serum albumin. Test compounds for $\beta$-receptor assays were diluted in 0.4% (v/v) dimethyl sulfoxide (DMSO) and for $\alpha$-receptor assays were diluted in 1.0% (v/v) DMSO. For $\beta_1$, $\beta_2$, $\alpha_{1D}$-, and $\alpha_{2B}$-adrenergic receptor activity, compounds were tested at a single concentration (10 μM). For $\beta_3$-adrenergic receptors, compounds were serially diluted in DMSO and aliquoted into 96-well microtiter plates in assay buffer with IBMX. Reagents were purchased from MilliporeSigma (Burlington, Massachusetts) and CisBio (Bedford, Massachusetts).

For $\beta$-receptor assays, cyclic adenosine monophosphate (cAMP) accumulation was assessed by a time-resolved fluorescence reso- nance energy transfer (TR-FRET) immunoassay (CisBio cAMP Dynamic) following manufacture’s instructions. CHO-K1 cells expressing $\beta_1$-adrenergic receptors were incubated for 15 minutes at 37°C with vibegron, mirabegron, or control (isoproterenol); CHO cells expressing $\beta_2$-adrenergic receptors and HEK293 cells expressing $\beta_3$-adrenergic receptors were incubated for 20 minutes at 37°C with vibegron, mirabegron, or control (procaterol for $\beta_2$, isoproterenol for $\beta_3$). After incubation, cells were lysed by the addition of a detection buffer containing a europium-labeled cAMP tracer. Fluorescence was measured 1 hour following incubation at room temperature (excitation, 320 nm; emission, 620 and 665 nm). For each assay, a cAMP standard curve was used to convert fluorescence readings to cAMP levels. Assays for specificity were performed using 2 biological replicates for $\beta_1$ and $\beta_2$ and 3 biological replicates for $\beta_3$. Doses used to obtain half-maximal effective concentration (EC$_{50}$) ranged from 0.3 nM to 10 μM.

To test selectivity of vibegron and mirabegron to $\beta$-adrenergic receptors, inhibition of $\alpha_{1D}$ and $\alpha_{2B}$ was also assessed. HEK293 and CHO-K1 cells expressing $\alpha_{1D}$ and $\alpha_{2B}$-adrenergic receptors, respectively, were incubated with radioligand (0.60 nM [H]-prazosin for $\alpha_{1D}$ or 2.50 nM [H]-rauwolscine for $\alpha_{2B}$) and vibegron, mirabegron, or control inhibitor (0.88 nM prazosin for $\alpha_{1D}$ or 14 nM yohimbine for $\alpha_{2B}$) for 60 minutes at 25°C. Membranes were filtered and washed 3 times, and the filters were counted with a scintillation counter to determine binding. These radioligand binding assays were performed using 2 biological replicates for $\alpha_{1D}$ and $\alpha_{2B}$. Data are presented as the percent inhibition of control radioligands; criterion for significance was $\geq$50% stimulation or inhibition.

**Statistical analysis**

Significance criteria for the agonists (ie, vibegron and mirabegron at each $\beta$ receptor) was considered a $>$0% increase in cAMP relative to isoproterenol or procaterol. Percent activity was defined as the maximal response of the test compound concentration expressed as percentage of the maximal response to the full control agonist (isoproterenol for $\beta_1$ and $\beta_3$ or procaterol for $\beta_2$). EC$_{50}$ and maximum response ($\text{EC}_{\text{max}}$) values were determined by nonlinear least squares regression analysis. A gamma coefficient was calculated to determine the measure of association between $\text{EC}_{\text{max}}$ and EC$_{50}$. Comparison of activity was made between vibegron and mirabegron at each $\beta$ receptor.

**Results**

**$\beta$-Adrenergic receptor specificity**

$\beta_1$-adrenergic activity relative to isoproterenol was 0% and 3% for vibegron 10 μM and mirabegron 10 μM, respectively; $\beta_2$-adrenergic activity relative to procaterol was 2% and 15%. At a
concentration of 10 µM, which exceeds mean human C_{max} values of vibegron and mirabegron by >10 times, β_{3}-adrenergic activity relative to isoproterenol was 104% for vibegron and 88% for mirabegron. Neither vibegron nor mirabegron met the significance criterion for inhibition of α\textsubscript{1D} or α\textsubscript{2B}-adrenergic receptors. α\textsubscript{1D}-adrenergic activity relative to yohimbine was 3% and 20% for vibegron and mirabegron, respectively; α\textsubscript{2B}-adrenergic activity relative to yohimbine was 37% and 33%.

β\textsubscript{3}-Adrenergic receptor maximal effect and potency

The E_{max} for vibegron and mirabegron at the β\textsubscript{3}-adrenergic receptor was estimated to be 99.2% and 80.4%, respectively, relative to isoproterenol (Figure 1 and Table 1). Treatment of β\textsubscript{3}-adrenergic receptor–expressing HEK293 cells with vibegron, mirabegron, or isoproterenol resulted in concentration-dependent responses at β\textsubscript{3}-adrenergic receptors (Figure 2). The mean (SEM) EC_{50} values at the β\textsubscript{3}-adrenergic receptor were 2.13 (0.25) nM for vibegron and 10.0 (0.56) nM for mirabegron.

Discussion

β\textsubscript{3}-adrenergic receptors are highly expressed in bladder tissue and detrusor smooth muscle where they mediate relaxation to aid in bladder filling.\textsuperscript{17,18} However, the diverse expression patterns of β-adrenergic receptors, including the expression of β\textsubscript{1} and β\textsubscript{2} receptors on cardiovascular tissue (reviewed in Wachter et al\textsuperscript{19}), complicates the targeting of β-adrenergic receptors. In addition, early drug development programs of β\textsubscript{3}-adrenergic receptor agonists were marked by off-target toxicities associated with drug metabolism and adverse effects such as phospholipidosis,\textsuperscript{20} affirming the importance of the design of β-adrenergic receptor agonists that are highly specific for the β\textsubscript{3} subtype to avoid off-target effects. This knowledge informed the intentional design of vibegron and aimed to improve drug-like properties and receptor selectivity, as well as reduce adverse effects seen with earlier molecules targeting β\textsubscript{2}-adrenergic receptors.\textsuperscript{20,21} Such alterations in structure produced a compound that was highly specific and selective toward β\textsubscript{3}-adrenergic receptors.\textsuperscript{20,25}

In this study, direct comparison of vibegron and mirabegron activity showed considerable selectivity of both drugs at β\textsubscript{3}-adrenergic receptors. However, vibegron did not show any measurable β\textsubscript{1} activity and had low β\textsubscript{2} activity, whereas mirabegron

Table 1

| Parameter                      | Vibegron       | Mirabegron     |
|--------------------------------|----------------|----------------|
| E_{max}, %                     | 99.2 (1.8)     | 80.4 (1.8)     |
| CV                             | 1.8            | 2.3            |
| 95% CI                         | 95.1–103.4     | 76.1–84.7      |
| EC_{50}, nM                    | 2.0 (0.2)      | 3.4 (0.5)      |
| CV                             | 11.0           | 13.5           |
| 95% CI                         | 1.5–2.5        | 2.3–4.5        |
| Gamma coefficient              | 1.1 (0.1)      | 1.1 (0.1)      |
| CV                             | 10.9           | 13.1           |
| 95% CI                         | 0.8–1.3        | 0.8–1.4        |

CV = coefficient of variation; EC_{50} = half maximal effective concentration; E_{max} = maximum response.

* Relative to the full agonist, isoproterenol (control).
showed low $\beta_1$ and more $\beta_2$ activity compared with vibegron. These results are in line with prior studies assessing the selectivity and specificity of vibegron or mirabegron at $\beta_2$-adrenergic receptors. In 2 prior studies using transfected CHO cells, mirabegron showed low agonist activity at monkey and human $\beta_1$- and $\beta_2$-adrenergic receptors and high selectivity at $\beta_3$-adrenergic receptors$^{26,27}$; both studies showed a maximal response of mirabegron relative to isoprotrenaline at $\beta_3$-adrenergic receptors of 80%. As monkey $\beta_3$-adrenergic receptors have high homology with human $\beta_3$-adrenergic receptors,$^{26}$ these results are congruent with the maximum response of 80.4% seen in this study with mirabegron at human $\beta_3$-adrenergic receptors. Monkey bladder strips under potassium chloride stimulation or resting tension have also shown maximal relaxant effects with mirabegron of 89% and 82%, respectively, relative to papaverine (control)$^{28}$; similar maximal relaxant effects were seen using mirabegron with carbachol-precontracted human or rat bladder tissue (89% and 94%, respectively).$^{27}$ Prior reports in CHO cells transfected with human $\beta_3$-adrenergic receptors have shown that vibegron has a maximum response of 84% at $\beta_3$-adrenergic receptors and minimal activity at $\beta_1$- and $\beta_2$-adrenergic receptors. In the presence of human serum, however, the maximum response at $\beta_3$-adrenergic receptors was increased to 101% to 102%. Similarly high maximum responses of 82% to 108% with vibegron were seen for CHO cells transfected with rhesus monkey, rat, or dog $\beta_3$-adrenergic receptors. Although in vitro activity may not directly translate to clinical significance or reflect pathologic conditions, activity at $\beta_1$ receptors in vitro, for example, could indicate the possibility of in vivo activity on cardiac tissue, where $\beta_1$ is primarily expressed.$^{19}$

Given the expression patterns of $\beta$-adrenergic receptors, cardiovascular off-target effects at $\beta_1$- or $\beta_2$-adrenergic receptor agonists are a concern. In the EMPOWER and EMPOWER extension studies, adverse events of hypertension were reported in similar percentages of patients who received vibegron and placebo.$^{10,23}$ In a clinical trial to assess small changes in blood pressure and heart rate using ambulatory blood pressure monitoring, vibegron was not associated with statistically significant or clinically meaningful effects on blood pressure or heart rate in adults with OAB with or without preexisting hypertension.$^{28}$ Although no direct comparison of trials studying mirabegron and vibegron can be made, safety results from these randomized controlled trials, in combination with the high level of selectivity of vibegron at $\beta_3$-adrenergic receptors in this study, suggest that vibegron may be less likely than mirabegron to be associated with off-target effects on the cardiovascular system.

These results are limited by low statistical power because the assays for specificity were performed using 2 biological repli-
and PNM were employees of Urovant Sciences at the time the work was conducted. KM is an employee of DermaVant Sciences.

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