Pharmacological Profile of the Novel α-Adrenoceptor Antagonist KT-611 (Naftopidil)

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ABSTRACT — The pharmacological profile of a new alpha-adrenoceptor antagonist, KT-611 (naftopidil), was studied in vitro. In the dog mesenteric and carotid arteries and in the rabbit, guinea pig and rat thoracic aortae, KT-611 competitively inhibited α₁-adrenoceptor-mediated contractions induced by noradrenaline with pA₂ values ranging from 6.73 to 8.15. KT-611 also inhibited the postjunctional α₂-adrenoceptor-mediated contractions in the dog saphenous vein (pA₂ = 6.77) or dog basilar artery. However, the responses mediated through prejunctional α₂-adrenoceptors (rat vas deferens), β-adrenoceptors (rat atria), muscarinic receptors (guinea pig ileum) and 5-HT₂ receptors (dog mesenteric artery) were little affected by KT-611. KT-611 also inhibited the sympathetic adrenergic contraction evoked by electrical transmural stimulation in the dog mesenteric artery, and the inhibition was not relieved upon repetitive washing for 1 hour with the drug-free solution. ³H-prazosin and ³H-clonidine binding to the rat cortex membranes was inhibited by KT-611 with pKᵢ values of 7.69 and 5.75, respectively. These results suggest that KT-611 is an α₁-adrenoceptor antagonist with a weak antagonistic activity to postjunctional α₂-adrenoceptors.

Since α-adrenoceptors were classified into α₁- and α₂-subtypes, selective agonists and antagonists to each subtype have been found (1, 2). Phenylephrine and prazosin are respectively a representative agonist and antagonist for α₁-adrenoceptors, while clonidine and rauwolscine show relative selectivity toward α₂-adrenoceptors. α₁-Adrenoceptor-selective antagonists have been developed as anti-hypertensive drugs, because α₁-adrenoceptors in the blood vessels are exclusively distributed on the smooth muscle, and the antagonists inhibit postjunctionally the adrenergic responses without any prejunctional effect (3, 4). α₂-Adrenoceptors were originally found at prejunctional sites, but postjunctional distribution of this subtype has been recently demonstrated in some blood vessels (5, 6). This in turn suggests the possibility that the blockade of postjunctional α₂-adrenoceptors in addition to α₁-adrenoceptors may be more beneficial for the treatment of hypertension or other vascular disorders.

KT-611 (naftopidil; (±)-4-(0-methoxyphenyl)-α-[(1-naphthyloxy)methyl]-1-piperazine ethanol, Fig. 1) is a newly synthesized compound that shows a potent anti-hypertensive action in experimental hypertensive animal models (7). Especially, KT-611 produces a longer hypotensive effect than prazosin in DOCA-Salt hypertensive rats and renal hypertensive rats. Because sympathetic nerve activity is enhanced in such hypertensive animals, Kawasaki et al. (7) have suggested that the hypotensive action of KT-611 may be due to a blocking action of sympathetic responses. In order
to clarify this point, we examined the selectivity of KT-611 to α₁- and α₂-adrenoceptors in vitro.

MATERIALS AND METHODS

**Functional experiments**

Mongrel dogs of either sex (7–15 kg), male rabbits (2–3 kg), male guinea pigs (350–450 g) and male Wistar rats (270–350 g) were used. After being killed under pentobarbitone anaesthesia, the appropriate tissues listed in Tables 1 and 2 were isolated from the animals. The blood vessels were cut helically under a dissecting microscope, and then rubbed with filter paper to remove the endothelial cells in order to avoid the possible involvement of endothelium-derived relaxing factors in the mechanical response (8, 9). The guinea pig and rat ileum (longitudinal muscle), rat vas deferens (prostatic portion) and rat right atria were also used. Each strip was mounted vertically in an organ bath containing 20 ml of Krebs-Henseleit solution of the following composition: 112 mM NaCl, 5.9 mM KCl, 1.2 mM MgCl₂, 2 mM CaCl₂, 25 mM NaHCO₃, 1.2 mM NaHPO₄ and 11.5 mM glucose. The medium was equilibrated with a gas mixture consisting of 95% O₂ and 5% CO₂ (pH 7.4). The temperature of the bath medium was maintained at 37°C except in the experiments with rat atria (at 30°C). The tension was recorded isometrically through a force-displacement transducer. The preparations were equilibrated for 90 min before starting the experiments.

In the experiments with noradrenaline, desmethylimipramine (10⁻⁷ M), deoxycorticosterone acetate (5 × 10⁻⁶ M) and propranolol (10⁻⁶ M) were added to the bath solution to block neuronal and extraneuronal uptake of noradrenaline and to block β-adrenoceptors, respectively. When the responses to clonidine were recorded in the dog saphenous vein, the preparations were pretreated with 10⁻⁷ M phenoxybenzamine for 30 min and then washed repeatedly in order to eliminate the involvement of α₁-adrenoceptors (10). Noradrenaline or clonidine was cumulatively added, and α₁-adrenoceptor antagonists including KT-611 were treated 30 min before, and during, the construction of concentration-response curves.

For the electrical transmural stimulation of intrinsic nerves in the isolated dog mesenteric artery, guinea pig ileum and rat vas deferens (prostatic portion), rectangular pulses (0.3 msec duration, 10 V) were delivered through a pair of platinum-wire electrodes at 5 or 10 min intervals. Other stimulus conditions were a frequency of 10 Hz, 10 sec train duration in the dog mesenteric artery and the guinea pig ileum, and a single pulse in the rat vas deferens.

**Binding experiments**

Rat cerebral cortex was homogenized in 40 volumes of Tris-HCl buffer (50 mM, pH 7.7 at 25°C) using a Polytron (set 6.0, 2 × 15 sec). The homogenate was centrifuged at 62000 × g for 15 min, and the resulting pellet was washed twice by suspension in the original buffer and recentrifugation. The final pellet was resuspended in the original volume of buffer and utilized in the binding assay. The binding assay was performed according to the method described previously (11). Briefly, the membranes (10 mg tissue wet weight) were incubated for 30 min at 25°C with ³H-prazosin (0.46 nM) or ³H-clonidine (0.51 nM) and different concentrations of a displacer. The final incubation volume was 2 ml, and all assays were done in duplicate. The binding reaction was terminated by rapid filtration under
vacuum through Whatman GF/B filters with four 5-ml rinses with ice-cold buffer. The tissue-bound radioactivity retained on the filters was extracted with scintillation fluid and counted. Specific binding of $^3$H-prazosin and $^3$H-clonidine was defined as the binding displacable by $10^{-5}$ M phentolamine and (+)-noradrenaline, respectively. Protein determinations were performed by the method of Lowry et al. (12). Drug competition curves were analyzed by indirect Hill analysis according to the method (equation 11) of Weiland and Molinoff (13), and IC$_{50}$ values and Hill coefficients were estimated.

**Drugs**

KT-611 (naftopidil: (±)-4-(0-methoxyphenyl)-\(\alpha\)-[(1-naphthoxy)methyl]-1-piperazine ethanol) was donated by Toyo Jozo Co., Ltd. (Tokyo, Japan). The following drugs were purchased: (+)-noradrenaline bitartrate, (+)-isoproterenol hydrogen tartrate, yohimbine hydrochloride, deoxycorticosterone acetate, (±)-propranolol hydrochloride, phenoxybenzamine hydrochloride (Nacalai Tesque, Kyoto, Japan); human angiotensin II (Peptide Institute, Osaka, Japan); guanethidine sulphate (Tokyo-Kasei, Tokyo, Japan); tetrodotoxin (Sankyo, Tokyo, Japan); prazosin hydrochloride, clonidine hydrochloride,desmethylimipramine hydrochloride,carbachol, \(\alpha\),\(\beta\)-methylene ATP (Sigma, St. Louis, MO, U.S.A); 5-hydroxytryptamine creatinine sulfate (5-HT) (Merck, Darmstadt, Japan); $^3$H-prazosin (17.4 Ci/mmol) and $^3$H-clonidine (20.5 Ci/mmol) (NEN Research Products, Boston, MA, U.S.A).

**Statistical analysis**

Experimental values are given as a mean ± S.E.M. pA$_2$ values for \(\alpha\)-adrenoceptor antagonists were obtained according to the method described by Arunlakshana and Schild (14). Results were analyzed by Student's t-test, and a probability of less than 0.05 was considered significant.

**RESULTS**

**Effects on postjunctional \(\alpha_1\)-adrenoceptors**

In the dog mesenteric and carotid arteries and the rabbit, guinea pig and rat thoracic aortae, noradrenaline produced concentration-dependent contractions. These contractions were competitively inhibited by prazosin with the high pA$_2$ values (Table 1), suggesting that the responses are mediated through postjunctional \(\alpha_1\)-adrenoceptors (9). Figure 2 shows the effects of KT-611 on the concentration-response curves to noradrenaline in the dog mesenteric artery and the rat thoracic aorta, where KT-611 shifted the curves to the right in both the tissues. However, the extent of shift at a given concentration of KT-611 was slightly larger in the thoracic aorta than in the mesenteric artery, suggesting that the inhibi-

**Table 1.** pA$_2$ values and slope factors for KT-611 and prazosin in various blood vessels

<table>
<thead>
<tr>
<th></th>
<th>pA$_2$</th>
<th>slope</th>
<th>pA$_2$</th>
<th>slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>KT-611</td>
<td></td>
<td></td>
<td>Prazosin</td>
<td></td>
</tr>
<tr>
<td>Dog mesenteric artery</td>
<td>7.76 ± 0.09</td>
<td>0.96 ± 0.03</td>
<td>8.22 ± 0.08</td>
<td>0.85 ± 0.03</td>
</tr>
<tr>
<td>Dog carotid artery</td>
<td>6.73 ± 0.28</td>
<td>0.81 ± 0.06</td>
<td>9.62 ± 0.13</td>
<td>1.01 ± 0.04</td>
</tr>
<tr>
<td>Rabbit thoracic aorta</td>
<td>7.52 ± 0.10</td>
<td>0.90 ± 0.05</td>
<td>8.82 ± 0.03</td>
<td>0.96 ± 0.16</td>
</tr>
<tr>
<td>Guinea pig thoracic aorta</td>
<td>7.33 ± 0.12</td>
<td>0.83 ± 0.05</td>
<td>8.45 ± 0.17</td>
<td>0.96 ± 0.09</td>
</tr>
<tr>
<td>Rat thoracic aorta</td>
<td>8.15 ± 0.14</td>
<td>0.97 ± 0.03</td>
<td>9.89 ± 0.03</td>
<td>1.08 ± 0.02</td>
</tr>
<tr>
<td>Dog saphenous vein</td>
<td>6.77 ± 0.10</td>
<td>1.12 ± 0.04</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Mean ± S.E. of 5–7 experiments. aThe data were quoted from Muramatsu et al. (9). bThe dog saphenous vein was pretreated with $10^{-7}$ M phenoxybenzamine and the antagonism to the concentration-response curve of clonidine was examined. cPrazosin at $10^{-7}$ M had no effect on the contractile response to clonidine.
tory potency varied between both tissues. However, as the slopes of the Schild plots were not significantly different from unity, it seemed that KT-611 competitively inhibited the contractile responses to noradrenaline in all the tissues. Table 1 shows the pA₂ values and slope factors of Schild plots for KT-611 in five different arteries. pA₂ values for KT-611 varied between the tissues, ranging from 6.73 to 8.15.

Effects on postjunctional a₂-adrenoceptors
In the dog saphenous veins pretreated with \(10^{-7}\) M phenoxybenzamine, clonidine at concentrations over \(3 \times 10^{-9}\) M produced concentration-dependent contraction. This contraction was not inhibited by \(10^{-7}\) M prazosin, but was competitively inhibited by yohimbine (pA₂ = 8.70 ± 0.09, n = 7). KT-611 inhibited the concentration-response curves to clonidine (Fig. 3, left). Since the slope of Schild plot for the antagonist was 1.12 ± 0.04, the antagonism by KT-611 seemed to be competitive; the pA₂ value was estimated to be 6.77 ± 0.10 (Table 1).

In the dog basilar arteries also, KT-611 (\(10^{-6}\) and \(5 \times 10^{-6}\) M) inhibited the noradrenaline-induced contraction. Figure 4 shows the representative results where KT-611 (\(5 \times 10^{-6}\) M) but not prazosin (\(10^{-7}\) M) attenuated the contractile response to \(10^{-5}\) M noradrenaline. Inhibitory ratios were 34 ± 6 (n = 4) and 72 ± 6% (n = 5) at \(10^{-6}\) and \(5 \times 10^{-6}\) M KT-611, respectively.

Effects on prejunctional a₂-adrenoceptors
In the prostatic portions of rat vas deferens, electrical stimulation (single pulse) produced a twitch contraction. This contraction was abolished after treatment with \(10^{-5}\) M \(\alpha, \beta\)-methylene ATP (n = 5), but was not affected by \(10^{-7}\) M prazosin (n = 5). Clonidine at concentrations over \(10^{-9}\) M attenuated the twitch
contraction, and the effect was competitively antagonized by yohimbine (pA2 value = 7.70, n = 5). KT-611 (10^-6 M) had no effect on the twitch contraction and the inhibitory effect of clonidine (Fig. 3, right).

In the guinea pig ileum, electrical transmural stimulation (at 10 Hz) produced a transient contraction. This contraction was abolished by 10^-6 M atropine. Clonidine attenuated the transient contraction, and the inhibition was antagonized by yohimbine (Fig. 5). KT-611 had no effect on the contractions induced by electrical stimulation and the inhibitory effect of clonidine.

In the guinea pig ileum, electrical transmural stimulation (at 10 Hz) produced a transient contraction. This contraction was abolished by 10^-6 M atropine. Clonidine attenuated the transient contraction, and the inhibition was antagonized by yohimbine (Fig. 5). KT-611 had no effect on the contractions induced by electrical stimulation and the inhibitory effect of clonidine.

**Guinea pig ileum**

![Fig. 5](image)

**Fig. 5.** Effects of KT-611 and clonidine on the neurogenic response to electrical stimulation in the guinea pig ileum. A: electrical transmural stimulation at 10 Hz for 10 sec.

**Effects on the sympathetic contractions in the dog mesenteric artery**

Electrical transmural stimulation (at 10 Hz) produced a transient contraction in the dog mesenteric artery. This contraction was completely inhibited by 10^-7 M tetrodotoxin or 3 x 10^-5 M guanethidine. KT-611 or prazosin inhibited the contractile response in a concentration-dependent manner, but did not abolish the responses (Figs. 6 and 7). Therefore, approximately 35% of the total response in amplitude remained as the residual component resistant to KT-611 or prazosin. Combined treatments with 10^-6 M KT-611 and 10^-6 M prazosin did not develop further inhibition. The residual component was abolished after treatment with 5 x 10^-6 M α,β-methylene ATP, suggesting that the residual component was purinergic response (15). The inhibition by KT-611 lasted even though the preparation was washed with the drug-free solution.

**Fig. 6.** Effects of KT-611 and prazosin on the contractile response to electrical transmural stimulation in the dog mesenteric artery. After treatment with 10^-6 M KT-611 or 10^-7 M prazosin, the preparations were washed with the drug-free solution, and the recovery was recorded 30 min and 60 min later. A: electrical transmural stimulation at 10 Hz for 10 sec.

**Fig. 7.** Concentration-inhibition curves on sympathetic neurogenic contraction by KT-611 (○) or prazosin (●). Experimental conditions are the same as those in Fig. 6. Sympathetic contraction before treatment with drugs was taken as 100%. Mean ± S.E. of 6–8 experiments.
solution for 1 hour. However, the inhibition by prazosin was relieved within 1 hour after prazosin removal.

**Effects on other responses**

KT-611 (10⁻⁶ M) had little effect on the contractile responses to 5-HT and KCl in the dog mesenteric artery, on the positive chronotropic response to isoproterenol in the rat right atria and on the contractile response to carbachol in the rat ileum. Table 2 shows the EC₅₀ values for various agonists before and after treatment with 10⁻⁶ M KT-611.

**Table 2.** EC₅₀ values of various agonists in the absence and presence of KT-611

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Agonist</th>
<th>Receptor</th>
<th>Control EC₅₀</th>
<th>10⁻⁶ M KT-611 EC₅₀</th>
<th>Ratio²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog mesenteric artery</td>
<td>noradrenaline</td>
<td>post, α₁</td>
<td>(1.3 ± 0.3) × 10⁻⁶ M</td>
<td>(4.7 ± 0.3) × 10⁻⁵ M</td>
<td>36</td>
</tr>
<tr>
<td>Dog saphenous artery</td>
<td>clonidine</td>
<td>post, α₂</td>
<td>(8.8 ± 0.8) × 10⁻⁹ M</td>
<td>(7.1 ± 0.8) × 10⁻⁸ M</td>
<td>8</td>
</tr>
<tr>
<td>Rat vas deferens</td>
<td>clonidine</td>
<td>pre, α₂</td>
<td>(3.3 ± 0.3) × 10⁻⁹ M</td>
<td>(4.3 ± 0.6) × 10⁻⁹ M</td>
<td>ns</td>
</tr>
<tr>
<td>Guinea pig ileum</td>
<td>clonidine</td>
<td>pre, α₂</td>
<td>(8.8 ± 0.9) × 10⁻⁹ M</td>
<td>(2.9 ± 0.4) × 10⁻⁸ M</td>
<td>3</td>
</tr>
<tr>
<td>Rat right atria</td>
<td>isoproterenol</td>
<td>post, β</td>
<td>(9.1 ± 1.4) × 10⁻⁹ M</td>
<td>(7.5 ± 0.7) × 10⁻⁹ M</td>
<td>ns</td>
</tr>
<tr>
<td>Rat ileum</td>
<td>carbachol</td>
<td>post, muscarinic</td>
<td>(1.0 ± 0.3) × 10⁻⁶ M</td>
<td>(1.3 ± 0.5) × 10⁻⁶ M</td>
<td>ns</td>
</tr>
<tr>
<td>Dog mesenteric artery</td>
<td>5-HT</td>
<td>post, 5-HT₂</td>
<td>(7.3 ± 3.3) × 10⁻⁷ M</td>
<td>(2.2 ± 0.6) × 10⁻⁷ M</td>
<td>3</td>
</tr>
<tr>
<td>Dog mesenteric artery</td>
<td>KCl</td>
<td></td>
<td>17.3 ± 1.0 mM</td>
<td>16.4 ± 1.3 mM</td>
<td>ns</td>
</tr>
</tbody>
</table>

Mean ± S.E. of 5–7 experiments. *EC₅₀ value in the presence of 10⁻⁶ M KT-611 was compared with that in the absence of KT-611 (control). ns: not significant.

**Table 3.** Parameters for the inhibition by alpha-adrenoceptor antagonists of specific ³H-prazosin and ³H-clonidine binding to rat cerebral cortex membranes

<table>
<thead>
<tr>
<th>Drug</th>
<th>³H-prazosin site</th>
<th>³H-clonidine site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kᵢ (nM)</td>
<td>nₜ⁺</td>
</tr>
<tr>
<td>Prazosin</td>
<td>0.145 (9.84)</td>
<td>0.99 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>(0.872 ± 0.095)</td>
<td></td>
</tr>
<tr>
<td>KT-611</td>
<td>20.5 (7.69)</td>
<td>1.07 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>(120.3 ± 12.3)</td>
<td></td>
</tr>
<tr>
<td>Yohimbine</td>
<td>177.4 (6.75)</td>
<td>1.02 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>(1044 ± 189)</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± S.E. of 3 experiments. Kᵢ values were calculated from the equation Kᵢ = IC₅₀/(1 + ³H-ligand/Kᵢ₀) for each drug, using the mean IC₅₀ and Kᵢ₀ values obtained from three separate experiments. The IC₅₀ values (shown in parenthesis) and Hill coefficients (nₜ⁺) were determined by indirect Hill analysis of the competition curves. B/A represents the ratio of the Kᵢ values for the antagonists at ³H-prazosin and ³H-clonidine sites. Mean ± S.E. of 3 experiments.
homogeneous with Hill coefficients of close to unity (Table 3). The \( K_i \) value of KT-611 was 20.5 nM (\( pK_i = 7.69 \)) for \(^3\)H-prazosin sites, whereas it was 1793 nM (\( pK_i = 5.75 \)) for \(^3\)H-clonidine sites. Thus, KT-611 had 87.5 times higher affinity to \( \alpha_1 \)-adrenoceptors than to \( \alpha_2 \)-adrenoceptors in the rat cerebral cortex.

**DISCUSSION**

KT-611 inhibited the concentration-response curves to noradrenaline in the dog mesenteric and carotid arteries and the rabbit, guinea pig and rat thoracic aortae. Schild plot analyses indicated that the antagonism for KT-611 is competitive because the slope factors were close to unity. As the contractile responses to noradrenaline in the above arteries have been reported to be mediated through \( \alpha_1 \)-adrenoceptors (9), KT-611 seems to have a competitive antagonistic action to \( \alpha_1 \)-adrenoceptors. A comparison with prazosin shows that KT-611 has approximately 10 times lower affinity to \( \alpha_1 \)-adrenoceptors but that the action is more durable. Therefore, the inhibitory action of KT-611 on sympathetic adrenergic contraction lasted even 1 hour after KT-611 removal. The long-lasting hypotensive effect of KT-611 has been recently reported in hypertensive animals (7).

In addition to its \( \alpha_1 \)-adrenoceptor-blocking action, KT-611 competitively inhibited the contractile response to clonidine in the dog saphenous vein (\( pA_2 = 6.77 \)) under conditions where the \( \alpha_1 \)-adrenoceptors were irreversibly blocked by phenoxybenzamine (10). KT-611 also attenuated the contractile response to noradrenaline in the dog basilar artery in which the response had been demonstrated to be caused through \( \alpha_2 \) but not \( \alpha_1 \)-adrenoceptors (5). These results suggest that KT-611 also has an antagonistic action to postjunctional \( \alpha_2 \)-adrenoceptors. Comparison of the \( pA_2 \) values between postjunctional \( \alpha_1 \) and \( \alpha_2 \)-adrenoceptors shows that KT-611 is 10–20-fold more selective to the \( \alpha_1 \)-adrenoceptors of dog mesenteric artery, rabbit, guinea pig and rat thoracic aortae.

In contrast to postjunctional \( \alpha_2 \)-adrenoceptors, prejunctional \( \alpha_2 \)-adrenoceptors were little affected by KT-611. Furthermore, the responses mediated through \( \beta \)-adrenergic receptors, muscarinic receptors and 5-HT receptors and the response to KCl were not inhibited by KT-611. From these results, it may be concluded that KT-611 is a selective antagonist to postjunctional \( \alpha_1 \)-adrenoceptors with an additional slight antagonistic activity towards the postjunctional \( \alpha_2 \)-adrenoceptor site.

This conclusion may be supported by the results obtained from the binding experiments. That is, \(^3\)H-prazosin binding in the rat cerebral cortex was effectively inhibited by KT-611, and the \( pK_i \) value of 7.69 (\( K_i = 20.5 \) nM) was well-consistent with the \( pA_2 \) values at \( \alpha_1 \)-adrenoceptors of the arteries tested. On the other hand, \(^3\)H-clonidine binding was antagonized by KT-611 with low affinity (\( pK_i = 5.75 \), \( K_i = 1793 \) nM). This affinity was approximately 10 times lower than the affinity at the postjunctional \( \alpha_2 \)-adrenoceptors of the dog saphenous vein (\( pA_2 = 6.77 \)). This discrepancy may reflect the different affinities of KT-611 to prejunctional and postjunctional \( \alpha_2 \)-adrenoceptors, because pharmacological resemblance of \( \alpha_2 \)-adrenoceptors in rat cerebral cortex and rat vas deferens has been reported (16).

Postjunctional distribution of \( \alpha_2 \)-adrenoceptors have been demonstrated in many blood vessels (5, 6, 17). Activation of the postjunctional \( \alpha_2 \)-adrenoceptors not only causes a direct contractile action but also enhances the responses to various contractile agents (5, 18, 19). Therefore, it is likely that, like KT-611, the drugs which have an antagonistic action to both postjunctional \( \alpha_1 \) and \( \alpha_2 \)-adrenoceptors may become more beneficial for the control of adrenergic responses in blood vessels and other tissues.

**Acknowledgment**

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