The Hypotensive Effect of 2-(5-Chloro-2-Phenoxyanilino)-2-Imidazoline (FR35447)

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Abstract—The hypotensive effect of FR35447 was comparable to that of prazosin and was more potent than that of hydralazine, but its duration of action was shorter. Repeated administration of FR35447 or prazosin to hypertensive rats for 5 consecutive days induced no significant difference in the intensity or duration of the hypotensive effect. In contrast, marked tachyphylaxis to hydralazine or phen tolamine was observed. FR35447 as well as prazosin induced only a transient increase in cardiac output in anesthetized dogs, whereas hydralazine induced a long lasting increase. This difference may contribute to no development of tolerance to FR35447 or prazosin. FR35447 decreased the pressor response to noradrenaline, but not that to angiotensin II or vasopressin in pithed rats, which indicates that FR35447 is an α-adrenoceptor antagonist. FR35447 has some selectivity for α2-adrenoceptors, but the selectivity was far less than that of yohimbine. Since FR35447 induced only slight hypotension following intracerebroventricular injection in anesthetized cats, the hypotensive effect of the drug does not appear to be mediated through the central nervous system. Whereas prazosin induced a dose-dependent increase in blood glucose in rats, FR35447 showed no significant effect.

Imidazoline derivatives are pharmacologically classified into several groups: α-adrenoceptor agonists, e.g., clonidine and naphazoline; α-adrenoceptor antagonists, e.g., phentolamine and tolazoline; and anti histaminics, e.g., antazoline. Extensive antihypertensive screening of various 2-imidazoline derivatives by our laboratories has resulted in the selection of 2-(5-chloro-2-phenoxyanilino)-2-imidazoline (FR35447) for further study (Fig. 1). As described in detail elsewhere (1), FR35447 has a protective effect on arachidonate-induced cerebral infarction in rats, whereas prazosin or hydralazine showed no significant improvement. The protective effect of FR35447 is presumed to be due to its free radical scavenging activity, synergistic effect on PGI2-induced inhibition of platelet aggregation, and/or increase in red cell deformability. We describe here the pharmacological properties of FR35447 as an antihypertensive agent.

Materials and Methods
Blood pressure and heart rate in conscious rats
Normotensive and three types of hypertensive rats were used. Normotensive rats: Male Wistar rats weighing 211–300 g with a mean blood pressure of 112–140 mmHg

![Fig. 1. Chemical structure of FR35447.](image-url)
were used. DOCA hypertensive rats: Male Wistar rats aged 5 weeks were nephrectomized unilaterally and maintained on 1% NaCl drinking water. Thirty mg/kg of deoxycorticosterone acetate (DOCA) suspended in peanut oil was given s.c. twice a week. Animals weighing 170–220 g with a mean blood pressure of 150–200 mmHg were used between 5 and 7 weeks after surgery. Renal hypertensive rats (two-kidney Goldblatt model): A silver clip, lumen width 0.22 mm, was applied to the left renal artery of male Wistar rats at 4 weeks of age. Animals weighing 172–300 g with a mean blood pressure of 160–238 mmHg were used between 6 and 14 weeks after surgery. Spontaneously hypertensive rats (SHR): Male SHR of the Okamoto-Aoki strain, more than 18 weeks of age and weighing 300–418 g, with a mean blood pressure of 150–210 mmHg were used.

**Single administration:** Blood pressure was measured with a pressure transducer through a polyethylene cannula inserted into the femoral artery and recorded on a polygraph. Heart rate was counted from the recording chart of blood pressure. The test drug or the vehicle (0.5% methyl cellulose) was given by a stomach tube to rats fasted for 18 hr before the experiment.

**Repeated administration:** A polyethylene cannula was implanted in the lower part of the abdominal aorta via the femoral artery. Three to four days after implantation, the experiments were started. The drug or the vehicle (0.5% methyl cellulose) was given orally by stomach tube to animals fasted for 3 hr before dosing once a day for 5 consecutive days. Blood pressure was measured on the 1st, 3rd and 5th days.

The experiments were conducted using groups of 5 animals.

**Blood pressure in anesthetized cats**

Intravenous injection: Mongrel cats of either sex weighing 2.3–5.0 kg were anesthetized with α-chloralose (50 mg/kg, i.p.) and urethane (250 mg/kg, s.c.). Intracerebroventricular injection: Mongrel cats of either sex weighing 2.1–4.0 kg were anesthetized with α-chloralose (50 mg/kg, i.p.). The head was fixed in a stereotaxic instrument, and a cannula was inserted to the lateral ventricle (Fr=13, L=3, H=7). The test drug solution (0.06 ml) or the vehicle (saline) was injected into the lateral ventricle at an injection speed of 0.03 ml/min. Blood pressure was measured through a cannula inserted into the femoral artery. The experiments were conducted using groups of 3–5 animals.

**Cardiac output and blood pressure in anesthetized dogs**

Mongrel dogs of either sex weighing 8.0–13.0 kg were anesthetized with pentobarbital-Na (35 mg/kg, i.p.). A flow meter probe was fitted to the aorta to measure cardiac output. Polyethylene cannulas were inserted in the femoral artery for measurement of blood pressure and in the saphenous vein for injection of drugs. The experiments were conducted using groups of 5 animals.

**Effect on pressor response to vasoactive agents in pithed rats**

Male Wistar rats weighing 214–317 g were used. Under ether anesthesia, a polyethylene cannula was inserted in the femoral artery to measure blood pressure and in the femoral vein to inject the drugs. The rats were pithed and artificially respired with room air. Before the experiment, the vagus nerves of the neck were sectioned and atropine methylbromide (1 mg/kg, i.v.) and dimethyl-tubocurarine iodide (1 mg/kg, i.v.) were given. In the experiment to test the selectivity on postsynaptic α₁ and α₂ adrenoceptors, propranolol-HCl (1 mg/kg, i.v.) was also given to counteract the β-adrenoceptor mediating effect. The dose-response curve to each vasoressor agent was obtained before and 5 min after i.v. injection of each test drug. The experiments were conducted using groups of 5 rats.

**Blocking activity on pre- and postsynaptic α-adrenoceptors in the isolated vas deferens of rats**

The vas deferens was removed from Sprague Dawley rats weighing 250–320 g. A 2 cm section, including mainly the central portion of the vas deferens, was excised and suspended in a 25 ml organ bath containing Krebs solution. When the twitch response to field stimulation was studied, the concentration of magnesium sulfate in Krebs solution was reduced by one half. The bath fluid was aerated with 95% O₂ and 5% CO₂. The
temperature of the bath fluid was maintained at 37 °C to study twitch response and reduced to 30°C to decrease spontaneous contractions when phenylephrine-induced contractions were studied. Contraction of the isolated preparations was measured with an isometric strain gauge and under a resting tension of 0.3–0.5 g.

Effect on presynaptic α-adrenoceptors: A platinum-electrode was placed at each end of the vas deferens. Continuous field stimulation was carried out at 0.2 Hz, 3 msec and 50–55 V. Clonidine, an α2 agonist, inhibits the twitch response of the field-stimulated vas deferens by acting on the presynaptic α-adrenoceptors. Blocking activity of α-antagonists was assessed by the antagonism of the α2-agonist, clonidine. Control dose-response curves and those in the presence of antagonist were obtained in separate preparations since full recovery from maximally effective concentrations of clonidine could not be obtained by washout. Each antagonist was added to the bath and allowed to be in contact with the vas deferens for 15 min prior to initiation of cumulative addition of clonidine.

Effect on postsynaptic α-adrenoceptors: Blocking activity on the postsynaptic α-adrenoceptors was assessed by the antagonism of phenylephrine-induced contractions. Dose-response curves to phenylephrine-HCl were obtained before and after addition of each antagonist.

Effect on plasma renin activity in rats
Male Wistar rats weighing 232–267 g were fasted for 18 hr. Under ether anesthesia, a polyethylene cannula was inserted in the femoral artery for collection of blood. One half ml of blood was withdrawn from the cannula before and 30 min after p.o. administration of the test drugs. The blood was mixed with 7.5 ml of 6% EDTA-Na2 and centrifuged at 3000 r.p.m. for 10 min (4°C). Plasma renin activity, measured by a radio immunoassay kit (CIS), was expressed as the amount of angiotensin I generated by incubating 1 ml of plasma for 1 hr. The experiments were conducted in groups of 5 animals.

Effect on urinary excretion of electrolytes and urine volume in rats
Male Sprague Dawley rats weighing 150–201 g were fasted for 18 hr. Immediately after oral administration of the test drug, 20 ml/kg of saline was loaded. The urine was collected for 6 hr. Urinary electrolytes (Na, K and Cl) were measured with a Stat/ION system (Technicon). The experiments were conducted in groups of 6–9 animals.

Drugs
FR35447, prazosin-HCl, hydralazine-HCl, phentolamine mesylate, clonidine-HCl and propranolol-HCl were examined. The doses used are expressed in terms of the respective salt.

Statistical analysis
Statistical differences between control and experimental groups were evaluated using Dunnett’s test (two tailed) after the analysis of variance.

Results
Effect on blood pressure and heart rate in conscious rats
FR35447 in p.o. doses of 0.1–0.32 mg/kg or more dose-dependently decreased blood pressure in conscious normotensive and DOCA, renal and spontaneously hypertensive rats. According to the ED30%, values (Table 1), which mean the doses required for 30% decrease in blood pressure, the hypotensive effect of FR35447 was comparable to that of prazosin and was more potent than that of hydralazine. However, as shown in Fig. 2, the duration was shorter. Clonidine showed a slight but long-lasting hypotension in low doses. High doses of the drug induced a dual effect: a short-lasting hypertension followed by a long-lasting hypotension.

FR35447 increased heart rate as did prazosin, but the effect was not as prominent
Table 1. Effect (ED₃₀%) of a single oral dose of FR35447 and other antihypertensive agents on mean arterial blood pressure in conscious rats (n=5)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Normotensive</th>
<th>DOCA</th>
<th>Renal</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR35447</td>
<td>0.74</td>
<td>0.24</td>
<td>0.92</td>
<td>0.46</td>
</tr>
<tr>
<td>Prazosin HCl</td>
<td>&gt;1.0</td>
<td>0.038</td>
<td>&gt;1.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Hydralazine HCl</td>
<td>2.2</td>
<td>0.8</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Clonidine HCl</td>
<td>&gt;10</td>
<td>5.8</td>
<td>&gt;10</td>
<td>0.48</td>
</tr>
</tbody>
</table>

ED₃₀%: dose (mg/kg) required for 30% decrease in blood pressure.

Fig. 2. Effect of oral administration of FR35447 and other antihypertensive agents on mean arterial blood pressure and heart rate in conscious spontaneously hypertensive rats. Symbols represent the mean change±S.E. of 5 rats. ○ Vehicle. ★ 0.01 mg/kg, ▼ 0.1 mg/kg, ● 0.32 mg/kg, ▲ 1.0 mg/kg, ◆ 3.2 mg/kg, ▽ 10 mg/kg.
as that of hydralazine. Clonidine decreased the parameter in a dose-dependent manner.

Repeated oral administration of FR35447 or prazosin, 1 mg/kg each, once a day for 5 consecutive days, to renal and spontaneously hypertensive rats caused hypotension and no tachyphylaxis appeared. In contrast, marked tachyphylaxis to hydralazine and phentolamine occurred (Table 2).

**Table 2. Effect of repeated oral administration of FR35447 and other antihypertensive agents on mean arterial blood pressure in conscious hypertensive rats**

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Change in B.P. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st day</td>
</tr>
<tr>
<td>Spontaneously hypertensive rats</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>-0.4 ±0.9</td>
</tr>
<tr>
<td>FR35447</td>
<td>-27.5**±5.5</td>
</tr>
<tr>
<td>Prazosin</td>
<td>-27.1**±5.3</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>-47.7**±1.8</td>
</tr>
<tr>
<td>Renal hypertensive rats</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>+4.5 ±2.3</td>
</tr>
<tr>
<td>FR35447</td>
<td>-29.0**±1.9</td>
</tr>
<tr>
<td>Prazosin</td>
<td>-31.4**±4.3</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>-34.7**±7.6</td>
</tr>
</tbody>
</table>

Test drugs were given once a day for 5 consecutive days. Each value represents the mean % change ± S.E. from the predosing level of the 1st day. n=5. *P<0.05, **P<0.01: significantly different from the vehicle group.

**Effect on blood pressure in anesthetized cats**

To determine if FR35447 causes hypotension through the CNS, the effect of intravenous and intracerebroventricular injection was compared. FR35447 caused a dose-dependent hypotension in i.v. doses of 0.01-1.0 mg/kg (data not shown). The hypotensive effect elicited by 1 mg/kg of the drug was almost the same as that by 0.1 mg/kg prazosin or 10 mg/kg hydralazine. Clonidine at an i.v. dose of 0.1 mg/kg induced transient hypertension followed by long-lasting hypotension (Fig. 3).

Following intracerebroventricular injection clonidine caused marked hypotension in doses of 1-100 μg/animal, whereas FR35447, prazosin and hydralazine had only a slight hypotensive effect (Table 3).

**Effect on cardiac output and blood pressure in anesthetized dogs (Fig. 4)**

Whereas FR35447 in i.v. doses of 0.1-1 mg/kg induced a dose-dependent hypotension, its effect on cardiac output was transient and dose-independent. Almost the same effect was obtained after injection of prazosin. In contrast to these two agents, hydralazine in doses of 0.1-10 mg/kg induced a long-lasting increase in cardiac output.

**Effect on pressor response to vasoactive agents in pithed rats**

The diastolic pressure of pithed rats prior
Table 3. Effect of intracerebroventricular administration of FR35447 and other antihypertensive agents on mean arterial blood pressure in anesthetized cats.

<table>
<thead>
<tr>
<th>Dose (μg)</th>
<th>Change in B.P. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>Vehicle</td>
<td>-1.3±1.4</td>
</tr>
<tr>
<td>FR35447</td>
<td>10 0.5±0.6</td>
</tr>
<tr>
<td></td>
<td>100 -10.2±3.5</td>
</tr>
<tr>
<td>Prazosin</td>
<td>10 -6.9±0.9</td>
</tr>
<tr>
<td></td>
<td>100 -1.9±3.3</td>
</tr>
<tr>
<td></td>
<td>1000 -3.6±1.2</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>10 0.5±3.2</td>
</tr>
<tr>
<td></td>
<td>100 1.9±3.3</td>
</tr>
<tr>
<td></td>
<td>1000 3.6±1.2</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1 -8.7±4.8</td>
</tr>
<tr>
<td></td>
<td>10 -20.6±2.9**</td>
</tr>
<tr>
<td></td>
<td>100 -31.2±2.5**</td>
</tr>
</tbody>
</table>

Each value represents the mean % change±S.E. of 3-5 animals. *P<0.05, **P<0.01: significantly different from the vehicle group.

Fig. 4. Effect of intravenous injection of FR35447 and other antihypertensive agents on cardiac output and mean arterial blood pressure in anesthetized dogs. Symbols represent the mean values of 5 animals.

- Vehicle, □ 0.1 mg/kg, △ 1 mg/kg, ◊ 10 mg/kg.
to any drug treatment was 53.1±1.0 mmHg (mean±S.E., n=55). FR35447 at an i.v. dose of 1 mg/kg significantly inhibited the agonist-induced pressor response, but not the pressor response to angiotensin II or vasopressin (Table 4), suggesting that FR35447 is an α-antagonist.

To test blocking activity on postsynaptic α1- and α2-adrenoceptors, the effect on the pressor response to phenylephrine, noradrenaline and B-HT 933 was compared in pithed rats (Fig. 5 and Table 4). Prazosin (0.1 mg/kg, i.v.), a specific α1-antagonist, inhibited phenylephrine induced hypertension markedly, but showed no effect on pressor response to B-HT 933. In contrast to prazosin, yohimbine (1 mg/kg, i.v.), an α2-antagonist, selectively antagonized the pressor response to B-HT 933. After i.v. treatment with FR35447 (1 mg/kg), the dose-response curves to these agonists shifted in parallel to the right. This antagonistic effect of FR35447 was somewhat more marked towards α2-adrenoceptors.

Blocking activity on pre- and postsynaptic α-adrenoceptors in the isolated rat vas deferens (Table 5)

FR35447 displaced the dose-response curves of clonidine and phenylephrine to the right, and the pA2 values were 7.88 and 7.41, respectively. According to the pA2 values, the potency on presynaptic receptors (α2) was about 3 times greater than that on postsynaptic receptors (α1). On the other hand, the pA2 value of prazosin against phenylephrine-induced contraction was 8.31, and that against clonidine was 5.66. Prazosin had 447 times greater affinity on postsynaptic α1-adrenoceptors than on presynaptic α2-adrenoceptors. According to pA2 values against clonidine, yohimbine and phentolamine had almost the same activity on presynaptic α2-adrenoceptors as FR35447. Yohimbine preferentially antagonized the twitch inhibiting effect of clonidine, but

Table 4. Displacement of log dose-response curves for the increase in diastolic pressure of phenylephrine, noradrenaline and B-HT933 following i.v. administration to pithed, normotensive rats

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Phenylephrine</th>
<th>Noradrenaline</th>
<th>B-HT933</th>
<th>Angiotensin II</th>
<th>Vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR35447 (1 mg/kg)</td>
<td>22.4</td>
<td>28.6</td>
<td>40.7</td>
<td>0.64</td>
<td>0.55</td>
</tr>
<tr>
<td>Yohimbine (1 mg/kg)</td>
<td>1.50</td>
<td>3.00</td>
<td>22.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentolamine (1 mg/kg)</td>
<td>9.05</td>
<td>7.57</td>
<td>8.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin (0.1 mg/kg)</td>
<td>20.2</td>
<td>2.43</td>
<td>1.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The displacement of these curves by FR35447, yohimbine, phentolamine and prazosin, administered i.v. 5 min before, is shown. Shifts were calculated at the level of 40 mmHg increase. n=5. —: Not tested.

Fig. 5. Log dose-response characteristics with respect to the increase in diastolic pressure of pithed, normotensive rats induced by i.v. phenylephrine, noradrenaline and B-HT 933. ○ Before treatment. ▲ 5 min after FR35447 (1 mg/kg, i.v.). ▲ 5 min after prazosin (0.1 mg/kg, i.v.). ★ 5 min after yohimbine (1 mg/kg, i.v.). ★ 5 min after phentolamine (1 mg/kg, i.v.). Symbols represent the mean values±S.E. of 5 rats.
phentolamine is an $\alpha$-antagonist which has fairly equal affinities for both pre- and postsynaptic $\alpha$-adrenoceptors.

The decreasing order of selectivity for the presynaptic $\alpha$-adrenoceptors was: yohimbine > FR35447 > phentolamine > prazosin.

**Effect on plasma renin activity in rats**

As shown in Table 6, plasma renin activity significantly increased from 14.4 to 171.7 ng Ang I/ml/hr 30 min after oral administration of FR35447 (1 mg/kg). This elevation was completely suppressed by simultaneous administration of propranolol (10 mg/kg). Prazosin (1 mg/kg, p.o.) or hydralazine (10 mg/kg, p.o.) also caused a significant increase in plasma renin activity.

**Effect on urinary excretion of electrolytes and urine volume in rats**

As shown in Fig. 6, FR35447 had no effect in p.o. doses up to 1 mg/kg. Urine volume and
urinary excretion of electrolytes decreased to one half of the control in doses of 3.2–10 mg/kg. Prazosin showed the same tendency. Hydralazine in doses of 1–10 mg/kg decreased all parameters in a dose-dependent manner.

Effect on serum glucose level in rats
FR35447 up to 10 mg/kg had no effect on serum glucose level in rats. Prazosin caused a dose-dependent increase in p.o. doses of 1.0–10 mg/kg with a maximum increase at 10 mg/kg (Fig. 7).

Fig. 6. Effect of oral administration of FR35447 and other antihypertensive agents on urine volume and urinary excretion of electrolytes in rats. Symbols represent the mean values ±S.E. of 9 rats. ○ FR35447, △ prazosin, [ l hydralazine. *P<0.05, **P<0.01: significantly different from each vehicle group.

Discussion
FR35447 induced dose-dependent hypotension in several kinds of conscious rats. According to the ED30% value, which means the dose required for a 30% decrease in blood pressure, the effect of FR35447 was comparable to that of prazosin, a specific α1-adrenoceptor antagonist (2, 3), and was greater than that of hydralazine, a direct-acting vasodilator (4), whereas the duration of FR35447 was shorter than that of hydralazine or prazosin. With FR35447 or
prazosin, a moderate tachycardia appeared concomitantly with a fall in blood pressure, but the effect was not as prominent as that of hydralazine.

Administration of FR35447, as well as prazosin, to conscious renal and spontaneously hypertensive rats for 5 consecutive days induced no significant reduction in the intensity of the hypotensive effect. In contrast, marked tachyphylaxis to hydralazine and phentolamine appeared. The exact mechanism of tolerance to hydralazine is uncertain, but an increase in cardiac output and/or retention of Na and water seem to play an important role (5, 6). The increase in cardiac output as well as the increase in heart rate is thought to occur as a consequence of reflex sympathetic activation (4, 5). FR35447 or prazosin induced only a transient increase in cardiac output, whereas hydralazine induced a long-lasting increase in cardiac output in anesthetized dogs. This difference may contribute to no development of tolerance to FR35447 or prazosin. Hydralazine-induced retention of Na and water is thought to be a consequence of increased sodium reabsorption in the proximal tubules (7) which, at least in part, results from increased plasma renin activity (5). However, since FR35447 and prazosin as well as hydralazine increased plasma renin activity in rats, plasma renin activity was ruled out as a mechanism for no development of tolerance to FR35447.

Hydralazine significantly decreased urine volume and urinary sodium excretion at a p.o. dose of 1 mg/kg, but this dose showed no significant effect on the blood pressure of normotensive rats. Hydralazine in p.o. doses of 3.2 mg/kg or higher induced a significant hypotension. Although FR35447 also induced some decrease in urine volume and urinary sodium excretion, the threshold dose for these effects (3.2 mg/kg, p.o.) was ten times higher than the dose needed to induce the hypotensive effect (0.32 mg/kg, p.o.) in normotensive rats. These differences between hydralazine and FR35447 may influence the development of tolerance in blood pressure response.

FR35447 is chemically classified as a 2-imidazoline derivative as is clonidine, which is an \( \alpha \)-agonist, and causes hypotension through the CNS (8–10). However, since FR35447 showed no marked hypotensive effect when injected into the cerebral ventricle of anesthetized cats, the drug-induced hypotension does not appear to be via the CNS. Clonidine given peripherally showed marked hypertension, which was followed by long-lasting hypotension in conscious rats and anesthetized cats, whereas FR35447 caused no increase in blood pressure. Since clonidine-induced hypertension is thought to be produced by stimulation of peripheral \( \alpha \)-adrenoceptors (8–10), it appears that FR35447 does not have an agonistic effect on \( \alpha \)-adrenoceptors.

Since FR35447 inhibited the pressor response to noradrenaline but not to angiotensin II or vasopressin in pithed rats, FR35447-induced hypotension seems to be derived from its blocking activity on the \( \alpha \)-adrenoceptors.

The specific \( \alpha_1 \)-agonist prazosin selectively inhibited phenylephrine-induced contraction of the isolated rat vas deferens. In contrast, the selective \( \alpha_2 \)-agonist yohimbine (11) had a greater affinity for the presynaptic \( \alpha_2 \)-adrenoceptors, i.e., inhibition of the clonidine-induced inhibition of twitch. Phentolamine had fairly equal affinities for both \( \alpha \)-adrenoceptors. These results are consistent with the data reported by Shoji (12), although he used noradrenaline as a postsynaptic \( \alpha_2 \)-adrenoceptor agonist. The blocking activity of FR35447 on presynaptic \( \alpha_2 \)-adrenoceptors was somewhat greater than that on postsynaptic \( \alpha_1 \)-adrenoceptors. However, the selectivity was far less than that of yohimbine.

Recent reports suggest two populations of postsynaptic \( \alpha \)-adrenoceptors: one is susceptible to prazosin and the other resistant to prazosin but susceptible to yohimbine. These can be classified as \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors, respectively (13–15). Langer et al. (16) have proposed that the postsynaptic vascular \( \alpha_1 \)-adrenoceptors are located predominantly intrasynaptically, whereas the postsynaptic \( \alpha_2 \)-adrenoceptors are mainly extrasynaptic and readily accessible by circulating agonists. After i.v. treatment with FR35447 the dose-vasopressor response curves to all \( \alpha \)-agonists shifted in parallel to the right. The
antagonistic effect of FR35447 was somewhat more marked towards B-HT 933, an $\alpha_2$-agonist (17), but the selectivity was far less than that of yohimbine as was the result obtained in the isolated rat vas deferens.

Oral administration of prazosin was followed by a rise in plasma glucose in rats. This result is consistent with the data in patients with hypertension reported by Barbieri et al. (18). In contrast to prazosin, FR35447 showed no significant effect on blood glucose in rats.

In conclusion, FR35447 has a potent antihypertensive effect which seems to be derived from its blocking activity on the $\alpha$-adrenoceptors. Repeated administration of the drug induced no tachyphylaxis. Different from prazosin, FR35447 showed no significant effect on rat blood glucose.

References