In Vitro Effects of the New Calcium Antagonist Lacidipine

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ABSTRACT—The effects of lacidipine (LC), a new dihydropyridine calcium antagonist, were studied in comparison with those of nifedipine (NF) in isolated arteries of the dog (DG-AR) and isolated aorta (GP-AO), left and right atria (GP-LA, GP-RA) and ventricular papillary muscles (GP-PM) of the guinea pig. In DG-AR precontracted with high K⁺, LC and NF produced a concentration-dependent relaxation. The relaxant effect of LC was most potent in the basilar artery. The calcium antagonistic effects of LC was 8.7 and 2.1 times more potent than those of NF, in GP-AO and GP-LA, respectively. Thus, LC was about 4 times more selective towards vascular smooth muscles than NF. The negative chronotropic effects in GP-RA and the negative inotropic effect in GP-PM of NF were more pronounced than those of LC. NF was more potent in inhibiting the action potential of GP-PM than LC both in normal polarized and depolarized conditions. The effects of LC were long-lasting. These results suggest that LC is a potent, highly vascular-selective calcium antagonist with little cardiodepressant effects and as such may be suitable for the treatment of hypertension.

Keywords: Lacidipine, Nifedipine, Vascular smooth muscle, Cardiac muscle, Organ selectivity

Lacidipine, diethyl 4-[2-[3-{(E)-1,1-dimethylethoxy}-3-oxo-1-propenyl]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Glaxo, Berona, Italy), is a new dihydropyridine calcium antagonist with the chemical structure shown in Fig. 1, in which the 3,5 methylester in the dihydropyridine ring and NO₂ in position 1 of the benzene ring of nifedipine were substituted with ethylesters and a long chain 3-(1,1-dimethylethoxy)3-oxo-1-propenyl, respectively. The presence of a long chain is unique among the dihydropyridine calcium antagonists. In several smooth muscles preparations (1, 2), lacidipine was shown to produce a long-lasting calcium antagonistic effect. In the present study, calcium antagonistic effects of lacidipine were studied in the isolated dog arteries, isolated aorta, right and left atria and papillary muscles of the guinea pig in comparison with those of nifedipine to assess the organ selectivity and the cardiodepressant effects.

MATERIALS AND METHODS

Isolated canine arteries preparation

The mongrel dogs of either sex (9–17 kg) were anesthetized with thiopentobarbital (35 mg/kg, i.v.) and exsanguinated from the common carotid arteries. The basilar, coronary (large: main left circumflex artery; small: small branch of the anterior descending artery), mesenteric, renal and femoral arteries were isolated and cleaned free of excess tissues. Endothelium was removed by rubbing the luminal surface with a stainless bar. Each artery was cut into rings (2- to 3-mm-wide) and mounted in a 10-ml organ bath for recording the isometric contractions. The preparations were equilibrated at a resting tension of 0.5–2.5 g (basilar: 0.5 g, coronary-large: 1.0 g, coronary-small: 0.5 g, mesenteric: 1.0 g and femoral: 2.5 g). The bathing solution was Tris buffer (Tris) containing: 125 mM NaCl, 2.7 mM KCl, 2.0 mM CaCl₂, 1.2 mM MgCl₂,
11.0 mM glucose and 23.8 mM Trizma base (pH was adjusted to 7.4 at room temperature). It was continuously bubbled with O₂ gas at 35 ±0.1°C. The isometric contraction was measured by a force-displacement transducer (Toyo Baldwin T7-30-240, Tokyo) connected to a strain-amplifier (Sanei 6M81, Tokyo) and recorded on a servocoder (Graphtec SR6211, Tokyo). After confirmation of the reproducibility of contraction by 60 mM K+ Tris (high K+ during the 3–4 hr of the equilibration period, three doses of lacidipine and nifedipine were administered to the preparations at 2-hr intervals. The preparations were recontracted with high K+. Isosmotic high K+ was prepared by replacing NaCl with equimolar K₂SO₄.

Isolated aorta, left and right atria and papillary muscle preparations of the guinea pig

Male albino guinea pigs (250–450 g) were anesthetized with ether. The heart and thoracic aorta were quickly excised and cleaned free of excess tissues. The following three types of experiments were performed.

Calcium antagonistic action in the isolated aorta: The isolated aorta was cut into 2- to 3-mm-wide rings and was mounted in an organ bath for recording of the isometric contractions under a 1.0-g resting tension. The procedures used were as described above for the canine arteries. After confirmation of the reproducibility of contraction by 60 mM K⁺ Tris (high K⁺) during an accommodation period, the preparations were incubated with ethanol (solvent of the calcium antagonists) or calcium antagonists for 2.5 hr. Then, the preparations were incubated for 30 min in Ca²⁺-free high K⁺ medium with the drug. The preparations were washed with Ca²⁺-free high K⁺ Tris (including the drug). CaCl₂ was added to the bath cumulatively. The contraction produced by the last administration of high K⁺ was taken as 100 %, and the contractions induced by a cumulative application of CaCl₂ were expressed as a % of this value, and the pA₂ values were calculated by the following equation:

\[ pA_2 = -\log \left( \frac{B}{A \cdot A - 1} \right) \]

where A is the concentration of Ca²⁺ at which 50% of the maximum contraction was obtained without calcium antagonists, A’ is the concentration of Ca²⁺ at which 50% of the maximum contraction was obtained in the presence of calcium antagonists, and B is the concentration of calcium antagonists. Isoosmotic high K⁺ solution was prepared by replacing NaCl with equimolar KCl.

Calcium antagonistic action in the left atria: The procedure described by Pappano (3) was used. The atria were divided carefully into the right and left halves. The left atria were mounted in organ baths under a resting tension of 0.2–0.3 g. The bathing solution was Tyrode’s solution (Tyrode) of the following composition: 137 mM NaCl, 2.7 mM KCl, 1.9 mM CaCl₂, 1.0 mM MgCl₂, 11.9 mM NaHCO₃, 0.4 mM NaH₂PO₄ and 5.5 mM glucose; it was continuously bubbled with 95% O₂ + 5% CO₂ at a temperature of 35 ±0.1°C. The preparation was stimulated electrically at a frequency of 1 Hz with a square wave pulse of 1-msec duration and of a voltage approximately 30% above the threshold supplied by a square-wave stimulator (Nihon Kohden MSE-3, Tokyo) via a pair of silver plate electrodes between which the preparations were placed. The isometric contraction was recorded on a linearly recording thermostylus oscillograph (Watanabe WTR-281, Tokyo) with a force-displacement transducer coupled with a carrier-amplifier (Sanei N6882). After a 1-hr equilibration period in Tyrode, the bathing solution was switched to the high K⁺ (22.0 mM) Tyrode (high K Tyrode), and the stimulation frequency was reduced to 0.4 Hz (duration 5 msec). Under this condition, the preparation was depolarized, and the contraction disappeared in less than 2 or 3 min. After a further equilibration period of 45 min, 2 × 10⁻⁷ M isoproterenol (ISP) was added to the bathing solution. Contractile activities resumed in association with the appearance of calcium-dependent action potential. Ten minutes after ISP administration, the concentration of Ca²⁺ in the high K⁺ bathing solution was reduced to 0.6 mM, and the dependency of contractile tension on the Ca²⁺ concentration was examined by cumulatively increasing the concentrations of CaCl₂. Then the preparations were incubated either with ethanol or with lacidipine or nifedipine for 40 min, and the dependency of the contraction on Ca²⁺ was examined again by constructing another cumulative dose-response curve for CaCl₂, from which the pA₂ values were calculated.

Chronotropic and inotropic effects in guinea pig right atria and papillary muscles: The right atria and right ventricular papillary muscles were mounted in organ baths under resting tensions of 0.25 g and 0.1 g, respectively. The bathing solution was a Krebs-Henseleit solution (Krebs-Henseleit) containing: 118 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgSO₄, 25.0 mM NaHCO₃, 1.2 mM KH₂PO₄ and 12.0 mM glucose; the solution was continuously bubbled with 95% O₂ + 5% CO₂ and kept at a temperature of 35 ±0.1°C. The right atria, which retained spontaneous rhythm, was used to assess the chronotropic action of the calcium antagonists. The rate of the spontaneous contraction (heart rate) was recorded on a linearly recording thermostylus oscillograph with a force-displacement transducer and a carrier-amplifier. The papillary muscles were stimulated using the procedures as described for the left atria with a voltage approximately 20% above the threshold. All preparations were allowed to equilibrate for 1 hr. Changes in heart rate and contractile tension produced by lacidipine and nifedipine were recorded for 40 min.

Effects on the action potential of right ventricular papil-
Papillary muscles: The papillary muscle was mounted in a 1-ml perfusion chamber and continuously superfused at a flow rate of 9 ml/min with a Krebs-Henseleit bubbled with 95% O₂ + 5% CO₂ and kept at a temperature of 35°C. The preparation was stimulated electrically by a square wave pulse of 0.2-msec duration at a frequency of 0.5 Hz with a voltage of 4–5 times the threshold supplied by a square-wave pulse stimulator (Nihon Kohden SEN-6100). Transmembrane potentials were recorded with a glass capillary micro-electrode filled with 3 M KCl with an electrical resistance of 10–30 MΩ. The action potentials were displayed on a cathode-ray oscilloscope (Nihon Kohden VC7) and photographed by a long-recording camera (Nihon Kohden RCL-6101). The following electrophysiological parameters were evaluated: the maximal rate of upstroke of the action potential (V_max), action potential amplitude (APA), action potential duration at 50% repolarization (APD₅₀) and action potential duration at 90% repolarization (APD₉₀).

After recording the normal action potentials, the bathing solution was switched to high K⁺ (25 mM) Krebs-Henseleit, and calcium-dependent action potentials were induced by addition of ISP (10⁻⁶ M). Calcium antagonists were applied and changes in action potentials were recorded for 15–20 min. The concentration of the drug was changed at intervals of 40 min.

The animals were treated in accordance with the established rules for Animal Experiments of this University.

Drugs
Lacidipine (Glaxo) and nifedipine (Sigma, St. Louis, MO, USA) were dissolved in ethanol and diluted with distilled water. 1-Isoproterenol hydrochloride (Nikken Kagaku, Tokyo) was dissolved in distilled water. Throughout the experiment, calcium antagonists were protected from light.

Statistical analyses
All values are presented as the mean ± S.E. To evaluate the differences between the means, Student’s t-test was conducted, and a probability value of less than 0.05 was considered to be significant.

RESULTS

Isolated canine artery preparations
Figure 2 depicts the dose-dependent relaxation produced by lacidipine and nifedipine in isolated canine arteries. The preparations were left in contact with calcium antagonists for 2 hr because the relaxation by lacidipine was found to develop very slowly, becoming stabilized only after 2 hr. The relaxation by nifedipine stabilized after 30 min. However, the same incubation time was used even with nifedipine. As it was found that the contraction by 60 mM K₂SO₄ was stable at least for 6 hr, three doses of calcium antagonists were administered successively in a cumulative manner.

Dose-dependent relaxations were produced by lacidipine and nifedipine. The concentrations necessary for elicitation of 50% relaxation (IC₅₀) are listed in Table 1. The effect of lacidipine was the most potent in the basilar artery with an IC₅₀ of 0.41 nM, which was significantly lower than the IC₅₀ of nifedipine in the same artery (i.e.,

Table 1. IC₅₀ values (nM) of lacidipine and nifedipine in canine arteries (n=5)

<table>
<thead>
<tr>
<th>Artery</th>
<th>Lacidipine</th>
<th>Nifedipine</th>
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<tbody>
<tr>
<td>Basilar</td>
<td>0.41 ± 0.07</td>
<td>1.64 ± 0.14</td>
</tr>
<tr>
<td>Coronary-large</td>
<td>1.70 ± 0.45</td>
<td>2.69 ± 0.53</td>
</tr>
<tr>
<td>Coronary-small</td>
<td>2.18 ± 0.63</td>
<td>2.04 ± 0.34</td>
</tr>
<tr>
<td>Renal</td>
<td>3.37 ± 1.06</td>
<td>3.06 ± 0.56</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>3.60 ± 1.06</td>
<td>3.54 ± 0.43</td>
</tr>
<tr>
<td>Femoral</td>
<td>5.19 ± 1.19</td>
<td>8.52 ± 2.36</td>
</tr>
</tbody>
</table>
1.64 nM). The rank order of potency of lacidipine was: basilar > coronary > renal > mesenteric > femoral, and that of nifedipine was: basilar > coronary > renal > mesenteric > femoral, although the potencies in these arteries were somewhat similar to each other except for that of nifedipine in the femoral artery (IC50: 8.52). There were no differences in the relaxant effects of these two agents on the large and small coronary artery.

Isolated aorta, left and right artia and papillary muscle preparations of the guinea pig

Calcium antagonistic effects in the guinea pig aorta:
In a preliminary study, it was found that the contraction by CaCl2 became smaller 2, 3 or 5 hr after the start of the experiment. We, therefore, carried out the control-runs (ethanol-pretreatment) simultaneously with the drug-pretreated runs. As the degree of inhibition of Ca2+ contraction induced by lacidipine at an incubation time of 3 hr was found to be almost the same as that obtained at an incubation time of 5 hr, the time of incubation with lacidipine was set at 3 hr.

Figure 3 depicts the cumulative concentration-response curves for contractions induced in high K+ depolarizing solution by CaCl2, and the effects of lacidipine and nifedipine thereupon. The concentrations of these calcium antagonists that caused a rightward shift by about one order without significantly depressing the maximum responses were chosen. Lacidipine (3 × 10^{-10} M) and nifedipine (3 × 10^{-9} M) caused a shift to the right of the cumulative concentration-response curves for CaCl2. The apparent pA2 values for lacidipine and nifedipine were 10.19 and 9.25, respectively (Table 2). Thus, judging from the pA2 values, lacidipine was 8.7 times more potent as calcium antagonist than nifedipine in the guinea pig aorta.

Calcium antagonistic effects in guinea pig left atria:
Figure 4 depicts the cumulative concentration-response curves for contractions induced by CaCl2 in high K+ depolarizing solution and the effects of lacidipine and nifedipine thereupon. Lacidipine (3 × 10^{-8} M) and nifedipine (10^{-7} M) caused a shift to the right of the cumulative concentration-response curves for CaCl2. The pA2 values for lacidipine and nifedipine were 7.35 and 7.02, respectively (Table 2). Thus, lacidipine was 2.1 times more potent as a calcium antagonist than nifedipine in the guinea pig left atria.

| Table 2. pA2 values of lacidipine and nifedipine (n=5–14) |
|-----------------|---------------------|---------------------|
|                 | Aorta              | Left atrium         |
| Lacidipine      | 10.19              | 7.35 ± 0.05         |
| Nifedipine      | 9.25               | 7.02 ± 0.04         |

Fig. 3. Effects of lacidipine (3 × 10^{-10} M, ○) and nifedipine (3 × 10^{-9} M, □) on the concentration-response curves for CaCl2 in high K+ depolarizing solution (60 mM K+) obtained in guinea pig aorta. Contraction elicited by CaCl2 are expressed as a % of the maximum response. Symbols represent the mean ± S.E. (n=5–14). □: Control.

Fig. 4. Effects of lacidipine (3 × 10^{-8} M, ○) (panel A) and nifedipine (10^{-7} M, □) (panel B) on the concentration-response curves for CaCl2 in high K+ depolarizing solution (22 mM K+) in guinea pig left atria. Contraction elicited by CaCl2 are expressed as a % of the maximum response. Symbols represent the mean ± S.E. (n=5). □: Control.
pig left atria.

**Chronotropic and inotropic effects in guinea pig right atria and papillary muscles:** Table 3 summarizes the effects of lacidipine and nifedipine on the rate of beating of the right atria and the contractile tension of the papillary muscles. The rate of beating and the contractile tension before administration of drugs were 179±5 beats/min (n=5) and 0.53±0.14 g (n=5) in the lacidipine group and 163±4 beats/min (n=6) and 0.48±0.11 g (n=4) in the nifedipine group. There were no significant differences between these values. The negative chronotropic and inotropic effects of lacidipine were slight even at the maximum concentration that can be used: The rate of beating and the contractile tension were 87% and 56% of the values just before administration of the drug, respectively. The same dose of nifedipine induced cardiac arrest and a severe negative inotropic effect, the contractile tension becoming 8% of the value just before administration of the drug.

**Electrophysiological effects in guinea pig papillary muscles:** Table 3 summarizes the effects of 10^{-6} M lacidipine and nifedipine on the V_{max}, APA, APD_{50} and APD_{90} of the action potentials of the guinea pig papillary muscles. The V_{max}, APA, APD_{50} and APD_{90} before administration of the drugs were 180±4 V/sec, 123±0.4 mV, 156±1 and 187±2 msec (n=6), in the lacidipine group and 176±2 V/sec, 123±0.4 mV, 155±2 and 188±2 msec (n=6), in the nifedipine group. There were no significant differences between the respective parameters of the two groups. The onset of action of lacidipine and nifedipine was slow, the effects stabilizing only after 40 min with lacidipine and after 20 min with nifedipine. Lacidipine and nifedipine did not modify V_{max} and APA, but significantly decreased APD_{50} and APD_{90}. The reduction in APD_{50} and APD_{90} produced by lacidipine was slight, while the effects produced by nifedipine were remarkable.

Figure 5 depicts the effects of 10^{-7}-10^{-6} M of lacidipine and nifedipine on V_{max}, APA, APD_{50} and APD_{90} of the calcium-dependent action potentials. The V_{max}, APA, APD_{50} and APD_{90} before administration of drugs were 30±1 V/sec (n=8), 86±1 mV (n=9), 126±3 (n=9) and 141±3 msec (n=8) in the lacidipine group (n=6) and 32±1 V/sec (n=6), 89±1 mV (n=6), 122±2 (n=6) and 133±3 msec (n=6) in the nifedipine group. There were no significant differences between the respective param-

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**Table 3. Effects of 10^{-6} M lacidipine and nifedipine on heart rate, contraction and action potentials in normal Krebs-Henseleit solution**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>HR</th>
<th>Contraction</th>
<th>V_{max}</th>
<th>APA</th>
<th>APD_{50}</th>
<th>APD_{90}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacidipine</td>
<td>87±4**</td>
<td>56±9**</td>
<td>99±1</td>
<td>99±0.4</td>
<td>91±2**</td>
<td>93±1**</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>arrest</td>
<td>8±5**</td>
<td>100±1</td>
<td>100±0.2</td>
<td>67±2**</td>
<td>70±2**</td>
</tr>
</tbody>
</table>

Values are means±S.E.M. (n=4–6) plotted as a % of the initial values. HR, heart rate; Contraction, contractile tension; V_{max}, maximal rate of upstroke of the action potential; APA, action potential amplitude; APD_{50}, action potential duration at 50% repolarization; APD_{90}, action potential duration at 90% repolarization. **P<0.01: significantly different from the initial values.
sters of the two groups. Lacidipine produced a dose-dependent and significant decrease in $V_{max}$, APA, APD$_{50}$ and APD$_{90}$. They became 58, 89, 78 and 80%, respectively, of the control after $10^{-6}$ M lacidipine. Depressant effects on action potentials were more marked with nifedipine than with lacidipine. $V_{max}$, APA, APD$_{50}$ and APD$_{90}$ became 43, 96, 74 and 77%, respectively, of the control after $10^{-7}$ M nifedipine. After $10^{-6}$ M nifedipine, the papillary muscles no longer responded to electric stimuli.

DISCUSSION

According to a study conducted in the rabbit ear artery, the calcium-antagonistic effect of lacidipine was a little less marked but longer-lasting than that of nitrendipine (1, 2). In the same report, the relaxation of the rat aorta, colon and bladder and guinea pig trachea was observed with lacidipine. In the present study, we attempted to further clarify the pharmacological effects of lacidipine using the isolated canine arteries and the isolated aorta, left and right atria, and papillary muscle of the guinea pig. The potencies of actions of lacidipine in various arteries, differences of calcium-antagonistic effects between the vascular and cardiac tissues and the effects on the electrophysiological parameters were compared with those of nifedipine.

Both lacidipine and nifedipine relaxed various arteries. The rank order of potency of lacidipine was: basilar > coronary > renal > mesenteric > femoral. The IC$_{50}$ of lacidipine was the lowest in the basilar artery. The value was significantly lower than that of nifedipine in the same artery. The relaxation by nifedipine was much the same among several arteries except that the relaxant effect was weak in the femoral artery. The rank order of potency of nifedipine was similar to that reported by Shimizu et al. (4).

The calcium antagonistic effects of lacidipine and nifedipine were found to be about 690 and 180 times more potent in the aorta than in the atria in the present study. This finding is in agreement with the general belief (5–7) that as compared with the effects of the non-dihydropyridine calcium antagonists such as verapamil and dilazem, the effects of dihydropyridine calcium antagonists as represented by nifedipine are more potent in vascular tissue than in cardiac tissue. According to Nakayama and Kasuya (8), the dose ratio of flunarizine, a calcium antagonist with a high selectivity towards vascular tissue, for inhibition of $K^+$-contracture of the basilar artery and for inhibition of the isometric contraction of the papillary muscle was 1:625. Thus, the vascular selectivity of lacidipine was even greater than that of flunarizine. The degree of vascular selectivity varied among dihydropyridine calcium antagonists. For instance, the selectivity towards the vascular systems was about 4 times more potent with lacidipine than with nifedipine because the calcium antagonistic effects of lacidipine were 8.7 and 2.1 times more potent than those of nifedipine in the aorta and the atria, respectively. This vascular selectivity of lacidipine is equal to that of nitrendipine (2), but is lower than that of nicardipine which is about 16 times more selective than that of nifedipine (7).

The inhibition of the rate of beating of atria and the inhibition of contraction of papillary muscles of the guinea pig was less than 50% with $10^{-6}$ M lacidipine, the maximum concentration that can be used in the present study, indicating that the inhibitory effect of lacidipine on the normal cardiac muscles was very weak. Similar results were reported by Cerbai et al. in sheep Purkinje fiber (9). In contrast, $10^{-5}$ M nifedipine produced an arrest in the right atria and inhibited the contraction of papillary muscles more than 90%.

In the guinea pig papillary muscles, lacidipine and nifedipine did not produce a significant inhibition of the normal action potential except for a significant shortening of APD$_{50}$ and APD$_{90}$ produced by nifedipine. Lacidipine significantly and concentration-dependently inhibited $V_{max}$, APA, APD$_{50}$ and APD$_{90}$ of the calcium-dependent action potential. This is in harmony with the findings of Cerbai et al. (9) and Nabata (10) that the inhibitory effects of lacidipine and nifedipine on the action potential were more potent in depolarized muscle than in normally polarized muscle. The inhibition by lacidipine was about 10 times less potent than that of nifedipine (the inhibition by $10^{-6}$ M lacidipine was equal to that of $10^{-7}$ M nifedipine).

It is well known that dihydropyridine calcium antagonists block L-type calcium channels which are widely distributed in tissues, particularly in the heart and smooth muscle (11). Though the vascular selectivity of dihydropyridine calcium antagonists is obvious (5–7), the mechanisms by which this selectivity is brought about is not clear at present. According to a hypothesis, the vascular selectivity is due to the participation of the high affinity binding site in the inhibitory effect on the calcium channels of vascular tissues. In contrast, the inhibitory effect in intact myocardial cell is mediated through a low affinity site (12). Another hypothesis explains the selectivity on the basis of selective binding of dihydropyridine calcium antagonists to calcium channels under the depolarization condition (13). The inhibitory effects are stronger in vascular tissue because vascular smooth muscle has a more depolarized resting membrane potential than cardiac muscle; potentials are in the range of $-30$ to $-40$ mV (14). The fact that the effects of nitrendipine are potentiated in the depolarized state because of a significant increase in high affinity binding sites (15, 16) is consistent with the
second hypothesis. The finding of the present study that the cardiac action of lacidipine was potentiated when the preparations were exposed to a depolarizing solution is also in line with the second hypothesis. The selectivity of lacidipine found in the present study may also be explained by the fact that the resting potential of the cerebral microvessels is much lower than that of the peripheral vessels (17).

The vascular selectivity of dihydropyridine calcium antagonists (18) was found to increase as the lipophilicity of the compound increases. Thus, the higher lipophilicity may be another factor contributing to the higher vascular selectivity of lacidipine, a compound with a long chain in position 1 of the benzene ring.

There are different isoforms of the L-type channels (19). McKenna et al. (20) suggested the existence of a subtle modification in the structure of the calcium channels. However, our present knowledge is insufficient to decide whether the presence of isoforms can explain the differences among tissues. Further experiments are needed to clarify the mechanisms underlying the vascular selectivity of Ca"^{2+}" antagonists of the dihydropyridine type.

In vitro experiments conducted with rabbit ear and basilar artery (1, 2) have shown that the action of lacidipine is long-lasting. In in vivo experiments with conscious animals and experimental hypertensive animals (spontaneously hypertensive rats, salt-loaded Dahl-S rats and renal hypertensive dogs), the onset of the blood pressure lowering effect of lacidipine was very slow and the duration was long (1, 2, 21, 22). Lacidipine administered orally in conscious spontaneously hypertensive rats proved to be about 8 times slower in onset and about 4 times longer-lasting than nifedipine and nicardipine (2, 23). Our study confirmed the long-action of lacidipine. As just mentioned, lacidipine has a long chain in the position 1 of the benzene ring and has an oil/water partition coefficient of 14400 (M. Ogawa et al., Glaxo Japan, Tsukuba, personal communication), a value about 10 times higher than that of nifedipine, which was 1387 (24). Gaviraghi (25) and Godfraind and Salomone (26) presented a three-compartment model to explain the long duration of action. The model postulates a compartment with a lipid binding site (designated as the "proximate lipid") that is in contact with an aqueous compartment. As lacidipine is highly lipophilic, it would concentrate in this compartment to be continuously released into an aqueous compartment during the washout period. The aqueous compartment in turn delivers lacidipine to another compartment in which binding to protein (receptor) occurs.

The results obtained in the present study suggest that lacidipine is a potent, long-lasting calcium antagonist with a high vascular-selectivity and a weak cardiodepressant action and as such may be particularly suited for treatment of hypertension.

REFERENCES


