Opposite Central Cardiovascular Effects of Nifedipine and BAY k 8644 in Anesthetized Rats

Stephane Laurent, Xavier Girerd, Danita Tsoukaris-Kupfer, Monique Legrand, Anne-Marie Huchet-Brisac, and Henri Schmitt

SUMMARY The central cardiovascular effects of the calcium channel blocker nifedipine and the calcium channel activator BAY k 8644 were studied in anesthetized and ventilated normotensive Wistar-Kyoto (WKY) or spontaneously hypertensive rats (SHR). Both drugs were administered in a 1.5-μl volume into the lateral ventricle of the brain (i.c.v.) or into the cisterna magna (i.e.). The injection of vehicle alone (i.e. or i.c.v.) did not significantly change mean arterial pressure (MAP) or heart rate. Nifedipine (5 and 50 μg/kg) and BAY k 8644 (5 and 50 μg/kg) induced opposite effects on MAP when centrally injected. Nifedipine decreased MAP and induced a bradycardia (i.c.v.) or no change in heart rate (i.e.), and BAY k 8644 increased MAP without any significant change in heart rate (i.e. or i.c.v.). These effects were more marked with the highest dose of either drug. These effects seemed to be of central origin, since they were suppressed by ganglionic blockade by hexamethonium (100 mg/kg i.v.), whereas after hexamethonium the hypotensive and the hypertensive responses to intravenously injected nifedipine and BAY k 8644, respectively, were preserved. Bilateral vagotomy suppressed the bradycardia induced by i.c.v. administered nifedipine. Previously i.c.v. administered nifedipine (5 μg/kg) antagonized the pressor response to BAY k 8644 (5 μg/kg i.c.v.). Changes in MAP and heart rate were significantly more marked in SHR than in WKY. These results indicate that a calcium channel inhibitor and a calcium channel activator can modulate in opposite fashion central mechanisms involved in blood pressure control. (Hypertension 9: 132–138. 1987)

KEY WORDS • 1,4-dihydropyridine • calcium channel blocker • spontaneously hypertensive rats • central nervous system • BAY k 8644

Calcium channel blockers produce an in vitro direct depression of myocardial contractility and sinus node automaticity as well as relaxation of isolated coronary and peripheral blood vessels by inhibiting calcium influx into the cells. The direct effects of calcium channel blockers on cardiovascular function can be modified by their effects on the autonomic nervous system. Calcium channel blockers have been reported to act peripherally to decrease neurotransmitter release at the neuromuscular junction and to modulate carotid baroreceptor function. Some evidence suggests that calcium channel blockers influence the autonomic nervous system at the central level, thus altering cardiovascular function.

The calcium ion modulates release in the central nervous system of various neurotransmitters, such as noradrenaline, acetylcholine, or γ-aminobutyric acid, involved in the central control of blood pressure and heart rate (HR). In addition, calcium ion may regulate receptor sensitivity to some neurotransmitters.

Among calcium channel blockers, 1,4-dihydropyridines such as nifedipine are lipophilic substances and can easily cross the blood-brain barrier. Since specific receptors for dihydropyridines have been found in the brain, we examined in this study the effects on arterial pressure and HR of nifedipine administered into the lateral ventricle or the cisterna magna of pentobarbital-anesthetized rats. To facilitate conclusions about the involvement of the 1,4-dihydropyridine receptors, we compared these results with the effects of BAY k 8644, methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethyl-phenyl)-pyridine-5-carboxylate, administered in the same way. A 1,4-dihydropyridine structurally similar to nifedipine, BAY k 8644 has been shown to have effects opposite to those of nifedipine and has been referred to as a calcium channel blocker.
"activator." Cardiovascular responses to nifedipine and BAY k 8644 in normotensive Wistar-Kyoto rats (WKY) were compared with those observed in spontaneously hypertensive rats (SHR).

Materials and Methods

Male, 14-week-old normotensive WKY and SHR (Okamoto strain, IFFA-CREDO) weighing 300 to 350 g were anesthetized with pentobarbital (50 mg/kg i.p.). The trachea was cannulated, and the animals were artificially resired by means of a Palmer "ideal" 10 pump (London, England). Instantaneous pressure and mean arterial pressure (MAP) were recorded continuously from a femoral artery by means of a Statham P23Db pressure transducer (Oxnard, CA, USA) on two channels of a Gould-Brush 3302 recorder (Cleveland, OH, USA). The HR was counted from the pressure signal by means of a Gould-Brush tachograph and recorded on the third channel of the recorder. A femoral vein was cannulated with a polyethylene catheter for the administration of nifedipine, BAY k 8644, or hexamethonium bromide. For intravenous injection, 1.5 μl of nifedipine or BAY k 8644 solution was added to 0.1 ml of saline.

Central administrations of drugs were performed as previously described. Briefly, a stereotaxic instrument (La Precision Cinematographique Française, Paris, France) was used to prepare the rats for intracerebroventricular (i.c.v.) administration. The rat's head was inclined at a 45-degree angle. The skin and the muscles of the neck were incised and retracted to expose the occipito-atlanto membranous. Drugs were injected into the cisterna magna with a fine needle (outer diameter, 0.3 mm) connected to a microsyringe. A single injection was performed in each animal. In another group of animals, intracerebroventricular (i.c.v.) injections were performed through a cannula inserted into one of the lateral cerebral ventricles through a trephine hole drilled 2 mm lateral and 2 mm posterior to the bregma, at a depth of 3.5 to 4 mm from the top of the skull. All drugs were administered in a 1.5-μl volume for 1 minute. Arterial pressure and HR were recorded for 30 minutes following central administration.

To determine whether arterial pressure and HR responses to i.c.v. and i.c. administrations of nifedipine and BAY k 8644 were neurally mediated, we examined responses to nifedipine and BAY k 8644 in four groups of animals in each strain: 1) control (no pretreatment), 2) hexamethonium-pretreated (100 mg/kg i.v. 10 minutes before the injection of nifedipine or BAY k 8644), 3) reserpine-pretreated (5 mg i.p. 48 and 24 hours before experiments), and 4) bilaterally vagotomized rats.

Nifedipine, reserpine, and hexamethonium bromide were obtained from Sigma Chemical Company (St. Louis, MO, USA). BAY k 8644 was kindly provided by Dr. B. Garthoff of Bayer A.G., Wuppertal, Federal Republic of Germany. Nifedipine and BAY k 8644 were dissolved in 95% ethanol (vol/vol) and assiduously protected from light. In each strain, 95% ethanol alone was used as the control solution. Hexamethonium was dissolved in saline.

Maximal responses to intervention are expressed as changes in MAP or HR from baseline ± SEM. Statistical analysis was performed by means of a one-way analysis of variance followed by a Student's t test for unpaired data. A probability value of less than 0.05 was considered statistically significant. For multiple pretreatment comparisons (ganglionic blockade, pretreatment with reserpine, and bilateral vagotomy), a Student's t test corrected by Bonferroni's inequality was used.

Results

Control Experiments

Administration (i.c.v. or i.c.) of 1.5 μl of ethanol (vehicle) produced no significant alterations in MAP or HR for 30 minutes after infusion in either normotensive WKY or SHR when compared with preinjection levels.

Cardiovascular Responses to Nifedipine

Intracerebroventricular Administration

In normotensive WKY, i.c.v. administration of nifedipine, 5 μg/kg, did not significantly change MAP and HR, but a higher dose (50 μg/kg) induced a rapid and sustained (more than 15 minutes) fall in MAP without significant change in HR (Figures 1, 2; Table 1).

In SHR, nifedipine, 5 μg/kg, slightly but significantly lowered MAP as compared with that in control animals receiving ethanol. No change in HR occurred at this dose. A higher dose of nifedipine (50 μg/kg) induced a rapid (within 3 minutes) and sustained (more than 30 minutes) fall in MAP, while HR slowed progressively and plateaued at 20 minutes (see Figures 1 and 2; Table 1).

To determine whether blood pressure and HR responses to nifedipine, 50 μg/kg i.c.v., were neurally mediated in SHR, we examined responses to nifedipine after 1) ganglionic blockade by hexamethonium bromide, 2) adrenergic neuronal blockade by reser-
FIGURE 2. Changes in heart rate (HR) after administration of nifedipine, 5 μg/kg (△, △) or 50 μg/kg (●, ○), or vehicle (■, □) into the lateral ventricle of normotensive WKY (filled symbols) and SHR (open symbols). Values are means ± SEM. Asterisk indicates significant difference (p<0.05) between responses to nifedipine and to vehicle in each strain by one-way analysis of variance.

intravenously administered hexamethonium (5-100 mg/kg) dose-dependently lowered blood pressure and HR. Ten minutes after pretreatment with the maximum dose of hexamethonium (100 mg/kg i.v.), MAP and HR decreased (from 170±15 to 76±6 mm Hg and from 317±25 to 260±22 beats/min, respectively) and i.c.v. administration of nifedipine no longer induced a fall in MAP and HR. In another group of SHR, however, the hypotensive response to intravenously administered nifedipine (50 μg/kg) was preserved (nifedipine, 50 μg/kg i.v. without hexamethonium: from 166±13 to 132±16 mm Hg; n=5; after hexamethonium: from 54±12 to 24±12 mm Hg; n=5). In SHR pretreated with reserpine, MAP and HR were significantly lower (87±6 mm Hg and 242±13 beats/min, respectively) than values in control SHR, and i.c.v. administration of nifedipine (50 μg/kg) in these animals no longer induced a fall in MAP and HR, while intravenously administered nifedipine (50 μg/kg) was still able to decrease MAP (from 87±5 to 70±3 mm Hg; n=5, p<0.01). Bilateral vagotomy suppressed the bradycardic response to nifedipine, while the hypotensive response was preserved.

Intracisternal Administration

In normotensive WKY, nifedipine, 5 μg/kg, did not significantly change MAP and HR. Nifedipine, 50 μg/kg, lowered MAP for at least 25 minutes with no significant change in HR (see Table 1).

In SHR, nifedipine (5 and 50 μg/kg) induced a rapid (within 3 minutes) and sustained (more than 30 minutes) fall in MAP; however, no significant change in HR occurred (see Table 1). Ten minutes after administration of hexamethonium (100 mg/kg i.v.), MAP decreased (from 169±6 to 54±8 mm Hg), and i.e. administered nifedipine (5 μg/kg) no longer induced a fall in MAP.

TABLE 1. Effects of the Calcium Channel Blocker Nifedipine on MAP and Heart Rate After Administration into the Lateral Ventricle (i.c.v.) or the Cisterna Magna (i.e.) in Rats

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>MAP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Maximum change</td>
</tr>
<tr>
<td>i.c.v.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 8)</td>
<td>126±6</td>
<td>5±1</td>
</tr>
<tr>
<td>5 μg/kg (n = 5)</td>
<td>136±7</td>
<td>−2±3</td>
</tr>
<tr>
<td>50 μg/kg (n = 9)</td>
<td>126±8</td>
<td>−11±5*</td>
</tr>
<tr>
<td>SHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>169±9</td>
<td>4±3</td>
</tr>
<tr>
<td>5 μg/kg (n = 6)</td>
<td>180±4</td>
<td>−4±2*</td>
</tr>
<tr>
<td>50 μg/kg (n = 5)</td>
<td>161±8</td>
<td>−23±5†</td>
</tr>
<tr>
<td>i.e.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 5)</td>
<td>99±14</td>
<td>0±3</td>
</tr>
<tr>
<td>5 μg/kg (n = 6)</td>
<td>101±7</td>
<td>−2±6</td>
</tr>
<tr>
<td>50 μg/kg (n = 5)</td>
<td>102±6</td>
<td>−19±8†</td>
</tr>
<tr>
<td>SHR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>138±4</td>
<td>4±3</td>
</tr>
<tr>
<td>5 μg/kg (n = 5)</td>
<td>145±7</td>
<td>−18±2†</td>
</tr>
<tr>
<td>50 μg/kg (n = 5)</td>
<td>129±6</td>
<td>−24±5†</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*p < 0.05, †p < 0.01, comparison of nifedipine (5 or 50 μg/kg) responses to control (ethanol) responses in each strain at 20 minutes (one-way analysis of variance).
TABLE 2. Effects of Nifedipine (50 μg/kg) on MAP and Heart Rate After Administration into the Lateral Ventricle of Anesthetized SHR

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>MAP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Before nifedipine</td>
</tr>
<tr>
<td>None (n = 5)</td>
<td>161 ± 8</td>
<td>−24 ± 4</td>
</tr>
<tr>
<td>HXM (n = 6)</td>
<td>170 ± 15</td>
<td>−3 ± 3*</td>
</tr>
<tr>
<td>Reserpine (n = 6)</td>
<td>87 ± 6</td>
<td>−5 ± 3*</td>
</tr>
<tr>
<td>BV (n = 4)</td>
<td>164 ± 9</td>
<td>−43 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SEM. HXM = ganglionic blockade with hexamethonium (100 mg/kg i.v.); Reserpine = treatment with reserpine (10 mg/kg i.p.) 48 hours previously; BV = bilateral vagotomy.

* p < 0.017, comparison of nifedipine responses in pretreated groups to nifedipine responses in control group at 10 minutes (Student's t test modified by Bonferroni's inequality).

Cardiovascular Responses to BAY k 8644

**Intracerebroventricular Administration**

The i.c.v. administration of BAY k 8644 (5 and 50 μg/kg) did not change significantly MAP or HR in normotensive WKY, as compared with the effects produced by administration of ethanol (Table 3; Figure 3). In SHR, however, BAY k 8644 (5 and 50 μg/kg) significantly increased MAP (from 152 ± 9 to 169 ± 10 mm Hg; and from 152 ± 4 to 180 ± 9 mm Hg, respectively; p < 0.05). The maximal increase in blood pressure was observed 20 minutes after the i.c.v. injection and lasted 30 to 45 minutes (see Figure 3). No significant change in HR occurred.

Intravenously administered hexamethonium bromide (5–100 mg/kg i.v.) dose-dependently antagonized the increase induced by BAY k 8644 in MAP in SHR (data not shown). The highest dose of hexamethonium (100 mg/kg i.v.) fully antagonized the increase induced by BAY k 8644 (5 μg/kg i.c.v.) in MAP (Table 4) but did not change the hypertensive response to BAY k 8644 injected intravenously (5 μg/kg i.v. without hexamethonium: from 160 ± 6 to 188 ± 6 mm Hg; n = 5, p < 0.01; after hexamethonium: from 83 ± 4 to 133 ± 17 mm Hg; n = 5, p < 0.01).

In SHR, i.c.v. administration of nifedipine (5 μg/kg) slightly and transiently lowered blood pressure.
Changes in MAP after administration of the calcium channel activator BAY k 8644, 5 μg/kg (●, Δ) or 50 μg/kg (○, □) into the lateral ventricle of normotensive WKY (filled symbols) and SHR (open symbols). Values are means ± SEM. Single (p < 0.05) and double (p < 0.01) asterisks indicate significant differences between responses to BAY k 8644 and to vehicle in each strain by one-way analysis of variance.

The hypertensive response to BAY k 8644 (50 μg/kg i.c.v.) was significantly reduced by pretreatment with hexamethonium (100 mg/kg i.v.) or nifedipine (5 μg/kg i.c.v.; see Table 4). Pretreatment of SHR with reserpine suppressed the hypertensive response to i.c.v. administered BAY k 8644 (50 μg/kg) but did not change the hypertensive response to intravenously administered BAY k 8644 (50 μg/kg: from 90 ± 4 to 132 ± 4 mm Hg; n = 7).

Table 4. Effects of BAY k 8644 on MAP After Administration into the Lateral Ventricle of Anesthetized SHR

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>MAP (mm Hg) Before BAY k 8644</th>
<th>MAP (mm Hg) Maximum change</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAY k 8644, 5 μg/kg</td>
<td>153 ± 4</td>
<td>17 ± 5</td>
</tr>
<tr>
<td>HXM (n = 6)</td>
<td>152 ± 4</td>
<td>58 ± 9</td>
</tr>
<tr>
<td>Nifedipine (5 μg/kg i.c.v.; n = 5)</td>
<td>172 ± 4</td>
<td>169 ± 5</td>
</tr>
<tr>
<td>BAY k 8644, 50 μg/kg</td>
<td>152 ± 4</td>
<td>22 ± 6</td>
</tr>
<tr>
<td>HXM (n = 4)</td>
<td>162 ± 4</td>
<td>57 ± 9</td>
</tr>
<tr>
<td>Reserpine (n = 7)</td>
<td>86 ± 4</td>
<td>2 ± 1*</td>
</tr>
<tr>
<td>Nifedipine (5 μg/kg i.c.v.; n = 6)</td>
<td>179 ± 6</td>
<td>176 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SEM. HXM = ganglionic blockade with hexamethonium (100 mg/kg i.v.); reserpine = treatment with reserpine (10 mg/kg i.p.) 48 hours previously. *p < 0.025 (BAY k 8644, 5 μg/kg) or p < 0.017 (BAY k 8644, 50 μg/kg), comparison of BAY k 8644 responses in pretreated groups to BAY k 8644 responses in control group at 10 minutes (Student’s t test modified by Bonferroni’s inequality).

Cardiovascular Responses According to Strain

Cardiovascular responses to centrally administered nifedipine and BAY k 8644 were significantly more marked in SHR than in WKY. For instance, 15 minutes after i.c.v. administration of nifedipine (5 or 50 μg/kg), MAP had decreased by 1 and 9%, respectively, in the WKY, while in the SHR the same doses resulted in increases in blood pressure of 11 and 18%, respectively. Such a difference between WKY and SHR also was found after i.c. administration of nifedipine and BAY k 8644.

Discussion

Intraventricularly and intracisternally administered nifedipine and BAY k 8644 had opposite effects on MAP: the former decreased MAP, while the latter increased it. The hypotensive response to nifedipine was more marked in SHR than in WKY. The hypertensive response to BAY k 8644 was only significant in SHR.

The MAP and HR changes might have resulted from nonspecific mechanisms, such as the vehicle used or the osmolarity of the drug solutions. Possible effects of vehicle administration were ruled out, since administration of vehicle in the same volume as drug solutions did not alter either parameter. It appears very unlikely that responses to centrally administered nifedipine or BAY k 8644 were related to osmolarity of the solutions. Nifedipine and BAY k 8644 have very similar molecular weights; thus, for an equal amount dissolved in an equal volume the osmoralties of the solutions are similar.

Nifedipine (50 μg/kg i.c.v. or i.e.) induced a rapid and sustained decrease in MAP in WKY and SHR. In SHR, a smaller dose of nifedipine (5 μg/kg i.c.v. or i.e.) was able to decrease MAP. Since the same doses of centrally or intravenously injected nifedipine induced a similar fall in blood pressure (50 μg/kg i.c.v.: baseline, 161 ± 8 mm Hg; maximum change, −23 ± 5 mm Hg; n = 5; 50 μg/kg i.v.: baseline, 169 ± 14 mm Hg; maximum change, −26 ± 5 mm Hg; n = 6), we had to rule out a leakage of nifedipine across the blood-brain barrier.
brain barrier into the systemic circulation. The origin of nifedipine-induced hypotension was studied in SHR, in which the cardiovascular responses were more marked than in WKY. After ganglonic blockade with hexamethonium or noradrenergic neuronal blockade by reserpine, i.c.v. or i.c. administered nifedipine no longer induced a fall in MAP. This finding suggests that centrally administered nifedipine lowered blood pressure by decreasing the adrenosympathetic tone. Alternatively, the lack of blood pressure change could have been due to an already lowered baseline. This hypothesis is unlikely, since the hypotensive response to intravenously administered nifedipine was preserved after ganglonic blockade or pretreatment with reserpine. No tachycardia accompanied the hypotensive response to i.c.v. or i.c. administered nifedipine, as has been reported after oral or intravenous administration. On the contrary, i.c.v. administered nifedipine induced a sustained bradycardia. This finding suggests an interaction between centrally administered nifedipine and baroreceptor reflex function. Indeed, the bradycardia induced by nifedipine (50 μg/kg i.c.v.) seemed to be due to a centrally mediated increase in vagal tone, as it was prevented by bilateral vagotomy.

BAY k 8644 (5 or 50 μg/kg i.c.v. or i.c.) increased MAP in SHR but not in WKY. The rise in blood pressure was rapid in onset, reached a maximum at 20 minutes, and lasted 30 to 45 minutes. The hypertensive response to i.c.v. administered BAY k 8644 was shown to be due to a centrally mediated increase in sympathetic tone, as it was prevented by ganglonic blockade or pretreatment with reserpine. This explanation is all the more evident since 1) the already lowered baseline should have potentiated the pressor response and 2) the pressor response to intravenously administered BAY k 8644 was unchanged after hexamethonium or reserpine administration. No bradycardia occurred during the hypertensive response to i.c.v. or i.c. administered BAY k 8644 (see Table 3), as we observed after intravenously administered BAY k 8644 (50 μg/kg i.v.: maximum change in MAP, 46 ± 5 mm Hg; maximum change in HR, -8 ± 8 beats/min), which also suggests an interaction between centrally administered BAY k 8644 and the baroreceptor reflex function. In addition, i.c.v. administered nifedipine antagonized the pressor response to BAY k 8644 injected in the same way. These results afford new arguments for the central origin of the cardiovascular effects of centrally injected nifedipine and BAY k 8644 and suggest the involvement of specific dihydropyridine binding sites in these responses.

Our results are partially consistent with those of Higuchi et al., who reported an excitatory effect of i.c. administered nifedipine on the nucleus tractus solitarii, at the origin of a decrease in sympathetic tone, in normotensive urethane-anesthetized rats. However, they excluded an increase in parasympathetic tone, since the bradycardia was preserved after atropine administration or vagotomy. In conscious normotensive rats, Imai et al. reported a hypertensive and tachycardic response to i.c.v. administered nicardipine, another calcium channel inhibitor structurally similar to nifedipine. Such discrepancies might be explained by interactions between the anesthetics and central cardiovascular control mechanisms.

Receptors for calcium channel blockers have been found in the rat brain, and the calcium ion has been shown to be involved in the release in the central nervous system of various neurotransmitters, such as norepinephrine, acetylcholine, γ-aminobutyric acid, which influence the autonomic nervous system and alter cardiovascular function. Nifedipine and BAY k 8644 have been shown to decrease and enhance slow-action potentials, respectively, and BAY k 8644 has been referred to as a calcium channel activator. Taken together, these data suggest that central cardiovascular effects of nifedipine and BAY k 8644 are mediated by their respective inhibitory and excitatory effects on calcium entry influx at the level of the slow calcium channels present in the brain. In this way, nifedipine and BAY k 8644 might have decreased or increased, respectively, resting sympathetic nerve activity by an effect on the discharge rate of vasomotor neurons within the central nervous system.

Cardiovascular responses to centrally administered nifedipine and BAY k 8644 were more marked in SHR than in WKY. Ishii et al. have reported a 57% increase in the maximum number of binding sites for [3H]nifedipine (a dihydropyridine molecule similar to nifedipine) in brain membranes of SHR as compared with those in normotensive WKY. Whether this increase in the maximum number of binding sites reflects an increase in functional calcium channels and explains the increased responsiveness of SHR to the centrally administered calcium channel modulators nifedipine and BAY k 8644 remains to be determined. Further studies are needed to show that this phenomenon could play a role in the development or maintenance (or both) of high blood pressure in SHR.

In conclusion, our results indicate that centrally administered calcium channel activators or inhibitors may modulate in opposite fashion calcium-dependent mechanisms involved in the central control of blood pressure.

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138 HYPERTENSION VOL 9, No 2, FEBRUARY 1987

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