Effect of MK-801 on Focal Brain Infarction in Normotensive and Hypertensive Rats

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The effects of the noncompetitive \( N \)-methyl-\( d \)-aspartate antagonist MK-801 on infarct size and systemic variables after middle cerebral artery occlusion in spontaneously hypertensive and Fischer-344 rats were investigated. Two doses (0.5 and 5 mg/kg) administered before the induction of ischemia were studied. MK-801 significantly reduced the neocortical volume of infarction (by about 32% at both doses) in Fischer-344 rats and had no neuroprotective effects in the striatum. In contrast, MK-801 had no significant influence on either cortical or striatal infarcted volume in spontaneously hypertensive rats. The reduction or lack of MK-801-induced neuroprotection in spontaneously hypertensive rats, as compared with Fischer-344 rats, could be attributed to a reduced collateral supply in the marginal area due to differences in the morphology of the pial anastomoses and/or in the effects of ischemia and treatment on arterial pressure. These results may have major clinical implications since a great proportion of human strokes are associated with hypertension. (Hypertension 1992;19:40-46)

The focal cerebral ischemia induced in animals by occlusion of the middle cerebral artery (MCA) is the most relevant model of human stroke presently available.\(^1\)\(^-\)\(^3\) It is thus the experimental model of choice for therapeutic studies. The reproducibility of this model in the rat varies considerably depending on the rat strain used.\(^4\)\(^-\)\(^5\) The volume of infarction obtained is more reproducible in spontaneously hypertensive rats (SHRs) than in any other strain,\(^4\)\(^-\)\(^5\) which might suggest that SHRs are most appropriate for pharmacological studies. The association of arterial hypertension with focal cerebral ischemia in this strain is an additional valuable feature since it is often encountered in human pathology. We recently investigated the effects of a broad spectrum excitatory amino acid (EAA) antagonist, kynurenate, and an adenosine agonist, \( R \)-phenylisopropyl)adenosine, on the infarct volume induced by MCA occlusion in SHRs. Although these two compounds reduced infarct size after MCA occlusion in normotensive rats,\(^6\)\(^-\)\(^7\) they produced no significant reduction in infarct size in SHRs,\(^8\)\(^-\)\(^9\) This suggests that the responsiveness of SHRs to some neuroprotective drugs is different from that of normotensive rats. However, the studies on hypertensive and normotensive rats were not performed under strictly comparable experimental conditions. The present study was therefore undertaken to compare the pharmacological neuroprotection in SHRs and normotensive rats after MCA occlusion using exactly the same experimental design. The Wistar-Kyoto rat is usually used as the normotensive control for the SHR because of their close genetic background. However, the volume of infarction is highly variable in Wistar-Kyoto rats\(^4\) so that its use in pharmacological studies is precluded. Fischer-344 rats were used as the normotensive strain since these rats give a more reproducible infarction size than do other normotensive strains.\(^4\) The noncompetitive \( N \)-methyl-\( d \)-aspartate antagonist MK-801 is known to reduce infarct size after MCA occlusion in normotensive rats\(^10\)\(^-\)\(^11\); thus, this compound was selected as the reference pharmacological agent for assessing any differences in the responses of the two strains.

Methods

The experiments were performed on 53 male Fischer-344 rats and 60 male SHRs, 15–16 weeks old, weighing 290–330 g (Charles River, Saint-Aubin-lès-Elbeuf, France). The rats had free access to food and water before the start of the experiment. The neuroprotective and systemic effects of two doses (0.5 and 5 mg/kg) of MK-801 were investigated. The animals were randomly injected with either MK-801 dissolved in saline or saline alone (5 ml/kg i.p.) just after the induction of halothane anesthesia, approximately 30 minutes before MCA occlusion.
Induction of Focal Cerebral Ischemia

The rats were anesthetized with halothane (1.5%) in oxygen (Dräger, Lübeck, FRG). The left MCA was occluded by a subtemporal approach, essentially as described by Tamura et al. The rat was placed on its side, and a vertical incision was made between the left orbit and the external auditory canal. The temporal muscle was divided midway vertically and reflected forward and downward with a retractor. The left eye and the parotid gland were left in place, but the posterior half of the zygomatic bone was removed. The inferotemporal fossa was exposed under a surgical microscope (Zeiss, Oberkochen, FRG), and a small craniotomy was made using a dental drill (BienAir, Bienne, Switzerland). The dura was incised and reflected. The arachnoid was then divided on either side of the artery. Bipolar microcoagulation forceps (Dolley, Montrouge, France) were used to occlude the MCA from the point where it crosses the inferior cerebral vein to the superior aspect of the olfactory tract. The lenticulostrate arteries were also coagulated when possible. The MCA was severed to ensure the flow interruption. The skin was then sutured, anesthesia was discontinued (approximately 2 minutes after MCA occlusion), and the animals were returned to their cages. All experimental procedures were carried out in strict accordance with the National Institutes of Health guidelines. Experiments were performed under permit no. 727 from the French Ministry of Industry and Research.

Measurement of Infarct Volume

The experiments related to the two doses of MK-801 were performed consecutively, so that distinct control groups were specially designed for each of the treated groups, as recommended by Ginsberg and Busto. Four groups of rats were thus studied for each strain (Fischer-344 and SHR): 1) MK 5: group of rats given 5 mg/kg MK-801 (n=13 SHRs, n=9 Fischer-344 rats); 2) control 5: control group for MK 5 (n=13 SHRs, n=10 Fischer-344 rats); 3) MK 0.5: group of rats given 0.5 mg/kg MK-801 (n=9 SHRs, n=12 Fischer-344 rats); 4) control 0.5: control group for MK 0.5 (n=12 SHRs, n=9 Fischer-344 rats).

Infarcts were delineated by 2,3,5 triphenyl tetrazolium chloride (TTC) staining. The rats were anesthetized with halothane (2.5%) in oxygen 48 hours after the induction of focal cerebral ischemia. Heparin (200 IU) was injected into the saphenous vein. The rats were then perfused with 2% TTC in distilled water for 10 minutes via a catheter placed in the ascending aorta through the apex of the left ventricle. The perfusion pressure was 170 mm Hg in SHRs and 130 mm Hg in Fischer-344 rats. The brains were left in place for 30 minutes to ensure reduction of the TTC to a colored formazan by viable dehydrogenases. The brains were then carefully removed, cooled in isopentane (−20°C), and sectioned in a cryomicrotome (−20°C) (Bright, Huntington, England). Black and white photographs were taken every 0.5 mm at the infarct level. The areas of infarcted cortex and striatum were determined from these photographs with a computer-based image analyzer (Histopericolor, MS2I, St. Quentin en Yvelines, France). The infarct volume was calculated from the area of necrotic tissue at each brain level and the distance between succeeding slices (0.5 mm).

Measurement of Systemic Variables

To study the combined effects of MCA occlusion and MK-801 treatment on systemic variables, only one control group was used for each strain since the experiments related to the two doses of MK-801 were performed randomly.

A catheter was chronically placed in the femoral artery, under halothane anesthesia, 24 hours before MCA occlusion. The catheter was canalized subcutaneously to exit at the neck. Arterial blood pressure, blood glucose content (Boehringer, Mannheim, FRG), rectal temperature, arterial pH, and blood gases (Corning, Medfield, Mass.) were measured before and 1, 4, 24, and 48 hours after onset of ischemia.

Statistical Analysis

Striatal infarction analysis was performed after the rats had been sorted into separate subgroups, those that exhibited striatal infarction and those that did not. The numbers of animals in these subgroups were compared by a binomial test. The infarcted areas and volumes of the two control groups in each strain were compared with Student's t test. When not significantly different, the two control groups of each strain were pooled. One-way analysis of variance, followed by Tukey's test, was then used to assess the effects of MK-801 on infarction surface and volume and also to compare the systemic variables between the different groups. The changes in systemic parameters with time in each group were assessed by paired Student's t test. Values of p < 0.05 were considered significant. Data are presented as mean±SD except when specified.

Results

No postoperative deaths or seizures occurred in any group.

Stability and Reproducibility of Control Groups

All animals had infarction in the cortex. Only three of 47 SHRs had no infarction in the striatum. However, this number was not negligible in Fischer-344 rats (15 of 40). There were significantly fewer striatal infarctions in the MK 0.5 series of experiments (43%; control 0.5 and MK 0.5 groups) than in the MK 5 series (84%; control 5 and MK 5 groups). However, within each series, this occurrence was not significantly different between control and treated animals. Furthermore, the occurrence of striatal infarction had no significant influence on the volume of infarcted cortex in Fischer-344 rats (113±21 mm³ in rats with striatal infarction and 106±26 mm³ in rats without striatal infarction).
CONTROL
MK-801 0.5mg/kg
MK-801 5mg/kg
SHR
FISCHER
CORTEX
STRIATUM

**FIGURE 1.** Bar graph shows effects of MK-801 (0.5 and 5 mg/kg) on cortical and striatal infarcted volumes in rats subjected to middle cerebral artery occlusion. Number of animals corresponding to each group is indicated above each column. SHR, spontaneously hypertensive rats; Fischer, Fischer-344 rats. *Significantly different from control (p<0.05).

No significant difference between the volumes of infarction of control groups was measured, either in the neocortex or in the striatum, for each strain. In addition, no significant difference between the areas of infarction at each brain level of the two control groups was measured in each strain. Consequently, the control groups in each strain were pooled for further analyses and named control.

The coefficients of variation (SD/mean) in Fischer-344 (0.20) and SHR (0.22) control groups were comparable.

**Effects of MK-801 on Infarction**

All the rats given 5 mg/kg MK-801 were completely unreactive for at least 24 hours, whereas those given 0.5 mg/kg did not show any gross behavioral abnormalities.

The effects of MK-801 on infarction volume of SHRs and Fischer-344 are shown in Figure 1, and those on infarction area are shown in Figures 2 (cortex) and 3 (caudoputamen).

MK-801 did not significantly modify the infarct volume in the caudoputamen, either in Fischer-344 or in SHRs whatever the dose used. Accordingly, the areas of striatal infarction were not significantly different at each brain level among the three groups (control, MK 5, and MK 0.5) in both strains.

Neither dose of MK-801 (0.5 and 5 mg/kg) caused any significant change in the volume and area of cortical infarction in SHRs. However, either dose of MK-801 significantly reduced the volume of infarction by 32% in the cortex of Fischer-344 rats. Area analyses supported these results and allowed localization of the neuroprotection. MK-801 (0.5 and 5 mg/kg) significantly reduced the areas of infarction in the cortex of Fischer-344 rats, from level +1 mm to level -3 mm, relative to the bregma,15 (i.e., in the posterior part of the infarct).

The infarct volumes and areas in the striatum and cortex of rats given 0.5 mg/kg MK-801 and 5 mg/kg MK-801 were not significantly different.

**Systemic Variables**

The mean arterial blood pressure (MABP), arterial glucose content, body temperature, arterial pH, PaO2, and PacO2 in each group at different times before and after MCA occlusion are shown in Table 1. MABP decreased in the control groups of both strains after MCA occlusion. This decrease was significant at all times examined in control SHRs and at 1 hour after MCA occlusion in control Fischer-344 rats. MK-801 (5 mg/kg) induced a slight increase in MABP that lasted for at least 4 hours after MCA occlusion in all the groups studied, whereas MK-801 (0.5 mg/kg), as compared with saline, induced an increase in MABP only in normotensive rats. However, both doses of MK-801 did not significantly modify MABP as compared with saline in the long term. The arterial glucose content tended to decrease slightly over time in all SHR groups and in Fischer-344 rats treated with...
TABLE 1. Physiological Variables Measured in Fischer-344 Rats and Spontaneously Hypertensive Rats Before and at Various Times After Middle Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Time (hr)</th>
<th>MABP (mm Hg)</th>
<th>Glucose (g/l)</th>
<th>Temperature (°C)</th>
<th>pH</th>
<th>PaO2 (mm Hg)</th>
<th>PaCO2 (mm Hg)</th>
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<tr>
<td>Fischer-344</td>
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<td>90±2</td>
<td>40.0±1.3</td>
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<td>124±10</td>
<td>1.02±0.07</td>
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<td>7.39±0.04</td>
<td>88±3</td>
<td>40.4±1.6</td>
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<td>7.41±0.04</td>
<td>89±7</td>
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<td>0.99±0.12</td>
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<tr>
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<td>7.42±0.05</td>
<td>101±6</td>
<td>38.9±2.5</td>
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<tr>
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<td>88±4</td>
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<td>144±8†</td>
<td>0.97±0.17*</td>
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<td>95±27</td>
<td>48.0±3.0*†</td>
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<td>148±8*†</td>
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<td>7.38±0.05*</td>
<td>85±6</td>
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<td>7.41±0.03</td>
<td>106±15</td>
<td>32.7±7.0</td>
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<td>7.50±0.01</td>
<td>99±8</td>
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<td>89±9</td>
<td>40.6±3.2</td>
</tr>
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<td>Control</td>
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<td>165±17*</td>
<td>0.99±0.04</td>
<td>38.1±0.1</td>
<td>7.38±0.05</td>
<td>87±7</td>
<td>43.0±4.7</td>
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<tr>
<td></td>
<td>4</td>
<td>160±14*</td>
<td>0.87±0.06*</td>
<td>37.9±0.3</td>
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<tr>
<td></td>
<td>0</td>
<td>179±11</td>
<td>1.23±0.17</td>
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<td>7.41±0.06</td>
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<td>MK 0.5 mg/kg</td>
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<td>1.11±0.18</td>
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<td>172±16</td>
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<td>137±8*</td>
<td>0.85±0.05*</td>
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<td>7.40±0.04</td>
<td>107±34</td>
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</table>

Values are mean±SEM. In each strain, the influence of MK-801 (0.5 and 5 mg/kg, administered approximately 30 minutes before middle cerebral artery occlusion) was studied. MABP, mean arterial blood pressure; PaO2, arterial partial pressure of oxygen; PaCO2, arterial partial pressure of carbon dioxide; SHRs, spontaneously hypertensive rats.

*p<0.05, comparison with value at time 0 (i.e., before halothane anesthesia).

†p<0.05, comparison with value in the control group at the same time.

FIGURE 3. Line plots show effects of MK-801 (0.5 and 5 mg/kg) on the area of striatal damage at various stereotactic coronal planes relative to the bregma (level 0 mm). There was no significant difference in either strain. Data are mean±SEM. SHRs, spontaneously hypertensive rats.
MK-801 (5 mg/kg). The comparison to control groups did not reveal any major significant difference. The other systemic parameters did not change, except in Fischer-344 rats treated with MK-801 (5 mg/kg). In this group, there was a decrease in body temperature and hypoventilation (assessed by a decrease in pH and an increase in Paco₂).

Discussion

Occlusion of the rat MCA has been performed in many laboratories. The effects on infarction occurrence, location, and size vary greatly (see Ginsberg and Bustó for review). This variation may result from many factors, the most important being the surgical procedure, the rat strain, and also the supplier or even the specific batches. In the present study, the control groups in each strain were studied at different times but exhibited the same location and volume of infarction in both cortex and striatum, demonstrating that our model is highly reproducible. However, the occurrence of striatal infarction was not reproducible in Fischer-344 rats since the percent of rats exhibiting caudoputamen infarction in two series of experiments performed at different times were significantly different. However, the volume of infarction in the cortex was not influenced by the presence of striatal infarction.

The volume of infarction in normotensive rats was significantly reduced by both doses of MK-801 tested. This reduction occurred in the neocortex but not in the striatum. By contrast, neither dose of MK-801 significantly modified the volume and the area of infarction in SHRs at any brain level.

The reduction in infarct size (32%) induced by a pretreatment of MK-801 (0.5 and 5 mg/kg) in Fischer-344 rats in the present study agrees with that found by Park et al. (38%) with MK-801 (0.5 mg/kg) in Sprague-Dawley rats and by Bielenga (32%) with MK-801 (10 mg/kg) in Fischer-344 rats. The results of the present study add to the growing evidence that EAA antagonists reduce infarct size after MCA occlusion in normotensive animals. They indicate that 0.5 mg/kg MK-801 is probably sufficient to completely block the N-methyl-D-aspartate receptor-associated cation channel, since 5 mg/kg MK-801 has the same effect as 0.5 mg/kg MK-801. Our data indicate that MK-801 reduced infarct area only in the caudal part of the infarct. This is in agreement with the results of Park et al. in the rat but differs from those obtained in the cat, where the reduction occurred all along the rostrocaudal axis of the brain. The present results do not support the involvement of hypothermia in the neuroprotective effects of MK-801, suggested by the results of Buchan and Pulsinelli in the gerbil subjected to global ischemia. In the present study, 5 mg/kg MK-801 induced hypothermia but 0.5 mg/kg MK-801 did not, although both doses had similar neuroprotective effects in Fischer-344 rats.

The present results fail to show that pretreatment with MK-801 produces a significant reduction of infarct size in SHRs. However, the statistical power of the results indicates that a reduction in infarct size of about 25% could be present without leading to significance (α=5%, β=20%). Thus, the present results do not conflict with previous reports showing a small effect of MK-801 pretreatment in SHRs. Coyle reported a 15% reduction in infarct size by MK-801 (1 mg/kg) and Dirnagl et al. found a 6% (nonsignificant) reduction by MK-801 (5 mg/kg). By contrast, MK-801 posttreatment (2.5 mg/kg at 8 and 16 hours after MCA occlusion) plus pretreatment (5 mg/kg, 30 minutes before ischemia) produced significant (23%) decrease in infarct size.

These results with MK-801, together with those obtained with kynurenate and R(phenylisopropyl)adenosine, provide evidence of how much more difficult it is to ensure pharmacological neuroprotection in SHRs than in normotensive rats. In the present study, using the same experimental design in the two strains, we showed that the responsiveness of SHRs and Fischer-344 rats to MK-801 is different. The effects of MK-801 in SHRs and normotensive rats probably differ because of a combination of two phenomena. First, antagonism of EAA receptors may require a minimal level of blood flow to ensure neuroprotection, as suggested by Ozurt et al., since little or no reduction in infarct size was obtained in the striatum, which is an end-arterial territory. Second, the ischemic territory in which blood flow is above the putative threshold for EAA antagonist efficacy may be very restricted, or even absent, in SHRs. Both anatomic and functional findings may account for this latter phenomenon.

There are anastomoses between the middle, posterior, and anterior cerebral arteries at the pial level in the rat. These anastomoses enlarge, in normotensive rats and in hypertensive rats after MCA occlusion. However, the dilatation of pial anastomoses leads to restitution of blood flow and complete protection from infarction after MCA occlusion in young normotensive rats, whereas MCA occlusion leads to infarction in young SHRs or SHRSPs. Several features also point to the involvement of the collateral supply: the distance between pial anastomoses and the lesion border is proportional to the diameter of the anastomosis, the mean luminal diameter of pial arteries is smaller in SHRs than in Wistar-Kyoto rats, collateral dilatation is more impaired in hypertensive animals than in normotensive ones, and finally, blood flow in the territory of MCA after occlusion is lower in SHRSPs than in Wistar-Kyoto rats.

The differing changes in the arterial pressure of the two strains may also contribute to the reduction of the amount of salvageable tissue in SHRs. In the present study, the changes in MABP are the result of a reduction due to MCA occlusion (as in the control groups) and a transient increase due to MK-801 (treated groups versus controls). The decrease in MABP in the control groups and in the treated groups at 24 and 48 hours was higher in SHRs (about
30–40 mm Hg) than in Fischer-344 rats (about 10–20 mm Hg). This may have induced different changes in the pattern of blood flow in the ischemic territories of the two strains since the extent of area of severe hyperperfusion depends on arterial pressure, as a result of loss of autoregulation in these regions. The infarct size also depends on arterial pressure.

All taken together, we suggest that the gradient of blood flow reduction between the collaterals and the ischemic core is more abrupt in SHRs than in normotensive rats, due to anatomic and/or functional differences, resulting in a narrower ischemic zone within which blood flow is above the threshold for EAA antagonist efficacy.

By contrast, when the action mechanism of a drug includes a vasodilator effect, as does nimodipine, there is significant neuroprotection in SHRs, to the same extent as in normotensive rats, as recently reported by Jacewicz et al., who performed MCA occlusion in both strains with the same protocol. This indicates that the differing responsiveness of normotensive and hypertensive rats depends on the pathophysiological mechanisms involved.

In conclusion, the present study demonstrates that in our experimental conditions, SHRs and normotensive rats do not exhibit the same responsiveness to the antagonism of EAA neurotransmission after MCA occlusion. Knowledge of the hypertensive rat responsiveness to neuroprotective compounds may be of major importance for clinical therapy since a great proportion of stroke cases are associated with and related to hypertension. Our results emphasize that therapies that have been chosen on the basis of experiments on normotensive animals might not be effective in hypertensive patients.

Acknowledgment

We are indebted to Dr. Eric Thomson MacKenzie for having critically reviewed the manuscript.

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KEY WORDS • cerebral ischemia • spontaneously hypertensive rats • dizocilpine maleate • cerebral infarction
Effect of MK-801 on focal brain infarction in normotensive and hypertensive rats.
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Hypertension. 1992;19:40-46
doi: 10.1161/01.HYP.19.1.40

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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