Nicardipine Reduces Calcium Accumulation and Electrolyte Derangements in Regional Cerebral Ischemia in Rats

Moshe Hadani, MD, Wise Young, PhD, MD, and Eugene S. Flamm, MD

We studied the effects of the calcium channel blocker nicardipine on regional tissue Ca2+, Na+, K+, and water shifts in the brains of seven Sprague-Dawley rats after permanent occlusions of the middle cerebral artery. We also assessed the entry of [14C]nicardipine into the brains of five rats; the highest concentrations of [14C]nicardipine were in the infarcted area. Nicardipine treatment significantly reduced Ca2+ accumulation in the middle cerebral artery territory by 60% compared with six untreated rats 6 hours after arterial occlusion. Eight 125-μg/kg boluses of nicardipine given every 30 minutes starting 5 minutes after arterial occlusion also significantly reduced the Na+ and K+ shifts in the middle cerebral artery territory by 40% and 50%, respectively, 6 hours after arterial occlusion. Nicardipine appears to reduce Ca2+ accumulation more than it reduces Na+ and water accumulation and K+ loss. Our results suggest that a calcium channel blocker can protect brain tissues in a model of focal cerebral infarction by directly reducing Ca2+ entry into ischemic cells. (Stroke 1988;19:1125–1132)

Cerebral ischemia causes a rapid shift of Ca2+ from the extracellular spaces into cells, manifested by a fall in extracellular calcium ionic activity and an increase in total tissue Ca2+ concentration. Excessive entry of Ca2+ into cells has been called a "final common pathway of cell death". In addition to disrupting basic cellular functions for which Ca2+ acts as a messenger, an increase in intracellular Ca2+ concentration activates membrane phospholipases, which break down membrane phospholipids and release free fatty acids, particularly arachidonic acid. Metabolism of arachidonic acid produces prostaglandins and leukotrienes, which can further damage cell membranes. Reduction of Ca2+ entry has been proposed as a therapeutic approach for cerebral ischemia.

Nicardipine is a dihydropyridine calcium channel blocker that has been shown to prevent or reverse vasospasm in animals. This drug was recently tested in a clinical trial to assess its ability to prevent vasospasm in patients with subarachnoid hemorrhage and to reduce ischemic damage resulting from a reduction in cerebral blood flow. The results of that study show that nicardipine reduces the symptoms of vasospasm and improves neurologic outcome of the patients more than would be anticipated from the angiographic evidence of decreased vasospasm. Allen et al have reported similar results in patients treated with nimodipine. Their findings suggest that nicardipine and other calcium channel blockers may directly protect ischemic cells as well as improve blood flow to the brain. The effects of calcium channel blockers on ischemia have been attributed to reduced Ca2+ entry into ischemic cells.

We recently described changes in tissue ion concentrations and water content in rat brains after middle cerebral artery occlusion (MCAo). This model of regional cerebral ischemia produces infarcts centered in the frontoparietal cortex. Ischemic areas show a more than twofold increase in Ca2+ concentration, a threefold increase in Na+ concentration, a >50% loss of K+, and a marked increase in tissue water content at the infarct site. The amount of Ca2+ accumulated in ischemic areas provides quantitative estimates of Ca2+ entry into cells, the magnitude of Na+ and water accumulation in the brain reflect edema, and the K+ loss at the lesion site indicates cell loss. The effect of calcium channel blockers on postischemic tissue Ca2+ accumulation has not been examined before. Thus, we studied the effects of
nicardipine on changes in regional brain Ca²⁺, Na⁺, and K⁺ concentration and water content in the rat MCAo model. We measured concentrations of [¹⁴C]nicardipine in ischemic and normal brains to ascertain drug distributions.

Materials and Methods

Surgical Procedure

Twenty-one male Sprague-Dawley rats weighing 280–300 g were anesthetized with 30 mg/kg i.m. ketamine HCl and 6 mg/kg i.m. xylazine. The right femoral vein and artery were cannulated with small-diameter polyethylene catheters. The rats were ventilated through a tracheostomy with room air on a small rodent respirator. (Harvard Instruments, South Natick, Massachusetts). Arterial blood gases were monitored during the experiments. Blood pressure was continuously measured with a pressure transducer (Grass Instruments, Quincy, Massachusetts). The left middle cerebral artery (MCA) was exposed via a subtemporal cranieotomy (2 × 3 mm) made with a microdrill between the foramen ovale and the optic foramen. The dura was opened with a hooked 25-gauge needle. The proximal MCA trunk was coagulated and divided distal to the lateral striate branch where the MCA crosses the olfactory stria. Six hours after MCAo the rats were anesthetized with 40 mg/kg pentobarbital and decapitated. The brains were removed and frozen and were analyzed by atomic absorption spectroscopy for ion concentrations and radioactive determination of [¹⁴C]nicardipine distribution.

Experimental Groups

We divided the 21 rats into four groups.

Group 1. Seven rats were treated immediately after MCAo with 1 mg/kg nicardipine HCl (Syntex Laboratories, Palo Alto, California) administered intravenously over 4 hours as 125-µg/kg boluses in 200 µl saline every 30 minutes beginning 5 minutes after MCAo. The rats were decapitated 6 hours after MCAo, and the brains were analyzed for regional tissue Ca²⁺, Na⁺, and K⁺ concentrations and for water content.

Group 2. Six untreated control rats received 200 µl saline every 30 minutes for 4 hours beginning 5 minutes after MCAo. The rats were decapitated and the brains were analyzed as in Group 1.

Group 3. Five rats were treated immediately after MCAo with [¹⁴C]nicardipine HCl (Syntex Laboratories) (specific activity 17.13 mCi/mM). Labeled drug was given in the same fashion as the unlabeled drug in Group 1. Group 3 rats were decapitated 6 hours after MCAo, and the brains were analyzed for regional distribution of [¹⁴C]nicardipine.

Group 4. Three intact rats were given intravenous nicardipine in the same manner as Group 1; no MCAo was carried out in Group 4. The rats were decapitated and the brains were analyzed as in Group 1.

Analysis of Ion Concentrations and Water Content

Immediately after decapitation, the brains were removed and cooled at −85°C until firm for cutting. A 4-mm-thick coronal slice was cut with a double razor blade assembly 4 mm posterior to the frontal poles. From this slice, four samples from each hemisphere were obtained with a sharpened metal tube (i.d. 3 mm) from the frontoparietal cortex (Area 1), the frontaloparietal cortex (Area 2), the parasagittal cortex (Area 3), and the basal ganglia (Area 4); the sampling method has been described in detail. Infarcts were apparent in Area 1 of all rats by 6 hours after MCAo and were clearly visible on the cortical surface when 2 ml Evans blue was injected intravenously. Areas 3 and 4 were adjacent to the infarct.

The wet weight of each sample was obtained (Mettler Chemical Balance AE 163, Hightstown, New Jersey), and the samples were dried at 105°C for 24 hours. The samples were then transferred to a desiccating jar under vacuum for 20 minutes and weighed again to determine the dry weight. The samples were prepared for atomic absorption spectroscopic determinations of Ca²⁺, Na⁺, and K⁺ concentrations by digestion in 1 ml concentrated nitric acid, heating to 95°C, and then drying at 95°C. The residue was dissolved again in 1 ml concentrated nitric acid. For Na⁺ and K⁺ measurements, a 0.1-ml aliquot was taken from the residual solution and diluted with 10 ml deionized water; the Na⁺ and K⁺ concentrations of the diluted solution were measured by atomic absorption spectroscopy (Perkin-Elmer 2280, Norwalk, Connecticut). For Ca²⁺ measurements, the residual solutions were again dried at 95°C and heated at 550°C for 24 hours in a muffle oven (Thermolyne 1400, Thermolyne Corp., Dubuque, Iowa); after cooling, 2 ml of 2.5% lanthanum oxide in 0.1N HCl was added. All atomic absorption spectroscopy measurements were bracketed with two standards, one containing only the diluent and the other containing known amounts of Ca²⁺, Na⁺, or K⁺. Flame conditions, detection wavelengths, and sampling rates were optimized for maximal sensitivity and linearity. Ca²⁺ absorption was measured at 422.7 nm, and Na⁺ and K⁺ absorptions were measured at 589.6 and 766.5 nm, respectively.

Tissue ion concentrations ([Ca]₀, [Na]₀, or [K]₀) are expressed as micromoles per gram dry weight. Since nicardipine treatment or MCAo may affect general brain ion concentrations in individual rats, we expressed changes in ion concentrations in the lesioned (left) hemisphere due to MCAo (Δ[Ca]₀, Δ[Na]₀, and Δ[K]₀) by subtracting the corresponding ion concentrations in homologous areas of the contralateral (right) hemisphere, reducing experiment-to-experiment variations in ion measurements or drug effects independent of MCAo. Tissue water content ([H₂O]₀) was calculated from tissue wet weight (W) and dry weight.
Analysis of $[^{14}\text{C}]$Nicardipine Distribution

Immediately after decapitation, the brains of the Group 3 rats were cooled for 10–20 minutes at $-85^\circ \text{C}$. A 4-mm-thick coronal slice was cut 4 mm behind the frontal poles and divided into its two hemispheres. The remainder of the cerebral hemispheres posterior to the slice was divided into two hemispheres. We also sampled the liver. The four brain and one liver samples were weighed on a chemical balance and digested in 1.5 ml of 1 M NaOH for 12 hours at room temperature. The solutions were then placed in scintillation vials containing a mixture of Aquasol, Protosol-ethanol, and acetic acid in a ratio of 4:1:1.

Radioactivity was counted on a Beckman LS 7500 liquid scintillation counter (Fullerton, California) for 10 minutes. Quench correction was performed by the method of external standard: channel ratio. Blood samples were drawn 1 and 6 hours after MCAo. Serum was obtained by centrifugation, a 200-μl aliquot was placed in a vial, and scintillation fluid was added as above; 30 mg $[^{14}\text{C}]$nicardipine powder contained 1 mCi. Tissue $[^{14}\text{C}]$nicardipine concentration was calculated as dpm/2200 = mCi/sample; $[^{14}\text{C}]$nicardipine/g tissue = nCi in sample × 30. Tissue and plasma concentrations of $[^{14}\text{C}]$nicardipine were expressed as nanograms per gram of wet weight and nanograms per milliliter of plasma, respectively.

Statistical Analyses

Differences in ion concentrations and water content between Groups 1 and 2 were analyzed by two-tailed t tests; $p<0.05$ indicated significance. Variance of mean ion concentrations and water content is given as standard deviation (SD); variance of mean changes in ion concentrations and water content is given as standard error of the mean (SEM). We used linear regression analysis to estimate the slope and correlation coefficient ($r$) of $\Delta[\text{Ca}^{2+}]$ vs. $\Delta[\text{Na}^+]$ and $\Delta[\text{Ca}^{2+}]$ vs. $\Delta[\text{H}_2\text{O}]$. Significance of the slope was calculated as

$$t = r\sqrt{(n-2)/(1-r^2)}.$$
TABLE 2. Ion and Water Concentrations by Hemisphere and Area in Rats Subjected to Middle Cerebral Artery Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Lesioned hemisphere</th>
<th>Contralateral hemisphere</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Area 1</td>
<td>Area 2</td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (µmol/g)</td>
<td>17.70±1.67*</td>
<td>13.85±3.22</td>
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<tr>
<td>Sodium (µmol/g)</td>
<td>691.5±162.4*</td>
<td>542.7±145.1</td>
</tr>
<tr>
<td>Potassium (µmol/g)</td>
<td>353.8±127.7</td>
<td>315.7±118.6</td>
</tr>
<tr>
<td>Water (ml/g)</td>
<td>5.21±0.53</td>
<td>4.40±0.44</td>
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<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
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<tr>
<td>Calcium (µmol/g)</td>
<td>22.65±4.58</td>
<td>16.20±7.39</td>
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<tr>
<td>Sodium (µmol/g)</td>
<td>938.1±180.8</td>
<td>680.8±224.8</td>
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<tr>
<td>Potassium (µmol/g)</td>
<td>167.4±52.2</td>
<td>231.8±90.3</td>
</tr>
<tr>
<td>Water (ml/g)</td>
<td>4.05±0.91</td>
<td>4.88±1.15</td>
</tr>
</tbody>
</table>

Data are mean±SD. Group 1, nicardipine-treated; Group 2, untreated controls, Area 1, frontoparyiform cortex; Area 2, frontoparietal cortex; Area 3, parasagittal cortex; Area 4, basal ganglia.

*p<0.05, *p<0.01, significantly different from untreated controls by t test.

(5.88 vs. 11.93 µmol/g dry wt, p<0.02, Figure 1). \( \Delta [Ca]_d \) in Areas 2–4 did not differ significantly (0.05<p<0.10) between groups although \( \Delta [Ca]_d \) appeared lower in Group 1.

Na⁺ accumulated significantly (p<0.001) in Areas 1 and 2 of the lesioned hemisphere by 6 hours after MCAo in Groups 1 and 2 (Table 2). In Area 1, \([Na]_d\) was significantly lower in Group 1 than in Group 2 (p<0.05, 692 vs. 938 µmol/g). Although Na⁺ also accumulated in Area 2 and to lesser extents in Areas 3 and 4, there were no significant differences between groups in these areas. \( \Delta [Na]_d \) in Area 1 was significantly lower in Group 1 than in Group 2 (460 vs. 698 µmol/g, p<0.05, Figure 2).

Large losses of K⁺ (p<0.001) occurred in Areas 1 and 2 of the lesioned hemisphere in Groups 1 and 2; minimal changes occurred in Areas 3 and 4 (Table 2). In Area 1, \([K]_d\) was higher in Group 1 than in Group 2 (354 vs. 167 µmol/g). \( \Delta [K]_d \) was only -158 µmol/g in Group 1 compared with -290 µmol/g in Group 2 rats (p<0.01, Figure 3). In Area 2, \( \Delta [K]_d \) was -197 µmol/g in Group 1 compared with -269 µmol/g in Group 2 rats; the differences in \( \Delta [K]_d \) between groups were not significant in Areas 2, 3, or 4.

Tissue water content increased significantly (p<0.01) in Areas 1 and 2 in the lesioned hemisphere by 6 hours after MCAo (Table 2). \([H_2O]_d\) in Area 1 was 6 ml/g in Group 2 and 5 ml/g in Group 1; although there appeared to be less water accumulation in Area 1 of Group 1 rats, the difference between \( \Delta [H_2O]_d \) in Groups 1 and 2 was not signifi-
Nicardipine Effects on Ions

A $[K]$d (nmol/gm dry, ipsi-contra)

![Figure 3](image)

**Figure 3.** Mean $-$ SEM (open bars) changes in potassium concentration ($\Delta [K]d$) calculated by subtracting dry-weight potassium concentration in unlesioned contralateral hemisphere from that in lesioned ipsilateral hemisphere in nicardipine-treated (filled bars) (n=7) and untreated control (shaded bars) (n=6) rats. $\Delta [K]d$ was significantly greater than 0 ($p<0.001$) in Areas 1 and 2 of both groups by 6 hours after middle cerebral artery occlusion. Nicardipine treatment significantly reduced $\Delta [K]d$ in Area 1 ($p<0.02$). Area 1, frontopyriform cortex; Area 2, frontoparietal cortex; Area 3, parasagittal cortex; Area 4, basal ganglia.

Significant (0.05<p<0.10, Figure 4). The differences in $\Delta [H2O]d$ between groups were not significant ($p>0.10$) in Areas 2, 3, or 4.

Relation of Ca$^2+$ to Na$^+$ and Water Shifts

We used linear regression analyses of $\Delta [Ca]_d$ vs. $\Delta [Na]_d$ and $\Delta [Ca]_d$ vs. $\Delta [H2O]_d$ to compare Groups 1 and 2 (Figures 5 and 6). In Group 2, $\Delta [Ca]_d$ related linearly to both $\Delta [Na]_d$ and $\Delta [H2O]_d$ with a significant $r$ of 0.866 ($p<0.01$) and 0.895 ($p<0.01$), respectively. Nicardipine treatment significantly decreased the slope of the relations by 27% and 22%, respectively, from 18.7 to 13.6 $\mu$mol Ca$^{2+}$/mmol Na$^+$ and from 4.9 to 3.8 $\mu$mol Ca$^{2+}$/ml water entry, suggesting that the drug had a greater effect on $\Delta [Ca]_d$ than on $\Delta [Na]_d$ and $\Delta [H2O]_d$. In the case of $\Delta [Ca]_d$ vs. $\Delta [Na]_d$, nicardipine treatment not only reduced the slope but had an r of 0.686, indicating that the relation was not significant (0.05<p<0.10). This difference in effects suggests that nicardipine treatment uncoupled the two ion shifts.

$[^{14}C]$Nicardipine Distributions

Both the lesioned and the contralateral hemispheres took up $[^{14}C]$nicardipine. Drug concentrations in areas of the lesioned hemisphere were significantly higher than those in homologous areas in the contralateral hemisphere (2.3 x $10^{-8}$ M [12.52 ng/g] and 0.8 x $10^{-8}$ M [4.42 ng/g], respectively, $p<0.01$). At the periphery of the infarct, $[^{14}C]$nicardipine concentrations did not differ from those in homologous areas of the contralateral hemisphere. By 6 hours after MCAo, liver $[^{14}C]$nicardipine concentrations were $10^{-6}$ M (534.8 ng/g) compared with plasma levels of $10^{-6}$ M (655.0 ng/ml) and $29.0 x 10^{-8}$ M (155.6 ng/ml) at 3 and 6 hours, respectively. In ischemic regions of the brain, $[^{14}C]$nicardipine concentrations were 2.3% and 8% of those in the liver and plasma.

Discussion

Our results indicate that nicardipine, administered intravenously in 125-µg/kg boluses at 30-minute intervals after MCAo in rats, reduced ion shifts at the infarct site. Nicardipine-treated rats had significantly less tissue Ca$^{2+}$ and Na$^+$ accumulation, as well as less K$^+$ loss, than untreated control rats 6 hours after MCAo. The treatment effects were most prominent in Area 1, the histologic center of the infarct. Since tissue Ca$^{2+}$, Na$^+$, K$^+$, and water shifts reflect cellular injury,13,15 our results suggest that nicardipine protected the infarct site.

At the outset of our experiments, we expected nicardipine to have little or no effect on Ca$^{2+}$ accumulation at the infarct site. If the drug had any beneficial effects, they should be most prominent in tissues surrounding the infarct, where nicardipine-induced vasodilation may improve collateral blood flow.9,10 Our data suggested otherwise. Although there was a trend toward less ion and water shifts in Areas 2, 3, and 4, the reductions in these areas were not consistent and were smaller than those in Area 1. It is important to confirm these findings with histologic assessments of infarct volume.

Decreased ion shifts may result paradoxically from a decrease in blood flow. Ion entry into and clearance from tissues depend on blood flow. If blood flow is reduced, ion shifts should be correspondingly less. For example, less blood flow will
result in less Ca\(^{2+}\) and Na\(^+\) brought to the tissue; likewise, less K\(^+\) would be lost from the tissue. Decreased blood flow must be considered since nicardipine reduced systemic blood pressure. However, we believe that hypotension and decreased blood flow are inadequate explanations of the reduced ion shifts for the following reasons. First, nicardipine-induced hypotensive periods were typically short and occurred only during the first 2 hours after MCAo. Second, decreased perfusion should affect Ca\(^{2+}\) and Na\(^+\) accumulation equally, but nicardipine had a significantly greater effect on Ca\(^{2+}\) accumulation than on Na\(^+\) accumulation.

We consequently sought an alternative explanation of our data. One possibility is that nicardipine blocks Ca\(^{2+}\) entry into ischemic cells and thereby limits Ca\(^{2+}\)-mediated cell damage. A rise in intracellular Ca\(^{2+}\) concentration should activate membrane phospholipases, which would result in a release of free fatty acids, particularly arachidonic acid. Irreversible membrane damage may result from degradation by phospholipases and byproducts of the metabolism of arachidonic acid to prostaglandins and leukotrienes.\(^{16,17}\) These byproducts are believed to contribute to cellular disintegration and death.\(^{18,19}\) Several investigators have proposed that blocking Ca\(^{2+}\) entry may prevent this cascade of events.\(^{20,21}\) Our results support this possibility by demonstrating that nicardipine treatment reduced Ca\(^{2+}\) accumulation by 60% and reduced Na\(^+\) and K\(^+\) shifts by 40% and 50%, respectively.

A perusal of the literature reveals conflicting reports concerning the effects of calcium channel blockers on cerebral ischemia models.\(^{22-26}\) For example, Roy et al\(^{25}\) found no improvement in regional cerebral blood flow with verapamil and diltiazem in cats subjected to permanent MCAo. A study of the dihydropyridine nimodipine in the rat MCAo model

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**Figure 5.** Scatterplot of relations between changes in dry-weight calcium concentration (\(\Delta[Ca^{2+}]_{d}\)) and changes in dry-weight sodium concentration (\(\Delta[Na^{+}]_{d}\)) by area 6 hours after middle cerebral artery occlusion for untreated control (CON) and nicardipine-treated (NIC) rats. Slope and correlation coefficient (r) of linear regressions are indicated. Slopes are significantly different. Note that r for NIC indicates that \(\Delta[Ca^{2+}]_{d}\) is not significantly correlated with \(\Delta[Na^{+}]_{d}\) (p<0.10). 1, frontopyriform cortex; 2, frontoparietal cortex; 3, parasagittal cortex; 4, basal ganglia.

**Figure 6.** Scatterplot of relations between changes in dry-weight calcium concentration (\(\Delta[Ca^{2+}]_{d}\)) and changes in dry-weight water content (\(\Delta[H_2O]_{d}\)) by area 6 hours after middle cerebral artery occlusion for untreated control (CON) and nicardipine-treated (NIC) rats. Slope and correlation coefficient (r) of linear regressions are indicated. Slopes are significantly different (p<0.05). 1, frontopyriform cortex; 2, frontoparietal cortex; 3, parasagittal cortex; 4, basal ganglia.
reported no effect on blood flow in the central core of ischemia, whereas blood flow in the periphery of ischemia increased.\textsuperscript{27} Unfortunately, these studies used reperfusion models, which are not comparable with permanent occlusion models. A recent double-blind study of nimodipine by Germano et al\textsuperscript{28} found a significant improvement in neurologic outcome and a reduction in infarct size 24 hours after MCAo in rats treated 1, 4, or 6 hours after occlusion. Although the best results were obtained in rats treated 1 hour after MCAo, Germano et al concluded that nimodipine had beneficial effects when administered up to 6 hours after the ischemic insult.

Three considerations complicate the interpretation of calcium channel blocker treatments in ischemia models. First, calcium channel blockers may improve blood flow without protecting the tissue against ischemia. For example, Harris et al\textsuperscript{29} found that although nimodipine slightly improved cerebral blood flow at the infarct site in primates with MCAo, the drug increased edema formation and electrolyte derangement. Failure of calcium channel blockers to protect the cells is often attributed to their failure to improve cerebral blood flow. Second, calcium channel blockers may protect tissues without improving blood flow. Third, in most previous studies, entry of a drug into the brain was not measured. Since most calcium channel blockers may not penetrate the blood–brain barrier well, the lack of a therapeutic effect may be due to insufficient drug entry.

We measured the concentrations of nicardipine in the brains of treated rats with and without MCAo. Our data indicates that nicardipine uptake was greater in the ischemic territory than in the surrounding or normal cortical tissues. Grotta et al\textsuperscript{30} have reported similarly greater uptake in ischemic cortical regions. The infarct site in Area I is also the region of greatest blood–brain barrier disruption after MCAo, as demonstrated by uptake of Evans blue.\textsuperscript{31} A nicardipine concentration of $2.3 \times 10^{-8}$ M is about twice that required to cause vasodilation.\textsuperscript{32} Most nicardipine was probably bound to cell membranes.\textsuperscript{33} For example, at 0.27 nM (100 times lower than the concentrations of nicardipine we found in Area I), 50% of the nimodipine is membrane-bound. Blood flow in the ischemic regions does not cease completely after MCAo. The finding that the greatest uptake of $[^{14}C]\text{nicardipine}$ occurred at the infarct site suggests that there was sufficient blood flow to bring the drug there.

Total tissue Ca\textsuperscript{2+} accumulation reflects Ca\textsuperscript{2+} entry into cells. Our experiments suggest that nicardipine reduces Ca\textsuperscript{2+} entry into ischemic cells. Nicardipine may reduce Ca\textsuperscript{2+} accumulation in ischemic tissue by directly limiting Ca\textsuperscript{2+} entry into ischemic cells. This is the most adequate explanation of our findings that nicardipine treatment reduced ion shifts most prominently at the infarct site and selectively reduced Ca\textsuperscript{2+} accumulation more than Na\textsuperscript{+} or water shifts. This pattern of ion shifts cannot be readily explained by improved collateral blood flow in the peri-infarct zone or by decreased blood flow at the infarct center due to hypotension.\textsuperscript{34} The spatial distribution of $[^{14}C]\text{nicardipine}$ suggests that the effects on ion shifts were greatest at the highest nicardipine concentrations.

It is possible that the greater effect of nicardipine on Ca\textsuperscript{2+} accumulation at the infarct site is a generic consequence of any therapy that reduces cellular mortality in stroke. Ca\textsuperscript{2+} accumulation may be a more sensitive reflection of tissue damage than Na\textsuperscript{+}, K\textsuperscript{+}, or water changes. This remains to be seen, however, since our particular approach has not been used to assess any other treatment in the rat MCAo model. In any case, these effects of nicardipine on ion shifts in this model were unexpected and they support the possibility that calcium channel blockers may act not only by improving blood flow but by directly reducing Ca\textsuperscript{2+} entry into ischemic cells. Our experimental approach may be useful for screening therapies of focal ischemia. Our method is straightforward and should be easily reproducible in any laboratory possessing an atomic absorption spectrophotometer.

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References


**KEY WORDS** • brain edema • calcium channel blockers • cerebral ischemia • nicardipine • rats
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