Chronic Treatment With a Low Dose of Lithium Protects the Brain Against Ischemic Injury by Reducing Apoptotic Death

Jihong Xu, PhD; Juraj Culman, MD; Annegret Blume, PhD; Stephan Brecht, MD; Peter Gohlke, PhD

Background and Purpose—In vitro and in vivo studies have demonstrated neuroprotective actions of lithium. The present study investigated the effect of a low dose of lithium on infarct volume and neurological outcome as well as on apoptotic and inflammatory processes in rats exposed to focal ischemia.

Methods—Cerebral ischemia was induced by middle cerebral artery occlusion (MCAO) for 90 minutes followed by reperfusion. Lithium (1 mmol/kg) was given subcutaneously daily for 14 days before the onset of MCAO and 2 days thereafter. Blood parameters and cerebral blood flow were assessed before, during, and after MCAO. Rats were examined for neurological deficits 24 and 48 hours after MCAO. Two days after MCAO, the brains were removed for immunohistochemical evaluation of caspase-3, terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL), activated microglia, and the expression of AP-1 proteins (c-Fos and c-Jun). Infarct volume was assessed by cresyl violet staining.

Results—Pretreatment with lithium did not alter cerebral blood flow or blood parameters. Neurological deficits were significantly decreased in rats treated with lithium at 24 and 48 hours after ischemia. Infarct volume was reduced in rats treated with lithium at 48 hours after ischemia. Lithium significantly decreased the ischemia-induced caspase-3 immunoreactivity and TUNEL staining as well as the AP-1 protein expression in the penumbra of the ischemic cortex. No changes in activated microglia were observed.

Conclusions—The present study demonstrates that chronic treatment with lithium at a low dose exhibits neuroprotection in transient focal cerebral ischemia. Antiapoptotic mechanisms are involved in the lithium-induced neuroprotective effects. (Stroke. 2003;34:1287-1292.)

Key Words: apoptosis ■ cerebral ischemia, focal ■ lithium ■ microglia ■ neuroprotection

Lithium is most widely used for treatment of manic-depressive illness. Increasing evidence supports the notion that lithium has neuroprotective effects both in vitro and in vivo. Lithium has been shown to protect against the toxic effects induced by a variety of insults, including glutamate, N-methyl-D-aspartate (NMDA) receptor activation, or toxic concentrations of anticonvulsants in rat cerebellar granule cells.1,2 Protective effects of lithium against the deleterious actions of glutamate and NMDA receptor activation have also been demonstrated in hippocampal and cortical neurons in culture.1 In a rat model of ischemia, chronic lithium treatment markedly reduced brain infarction and neurological deficits induced by permanent middle cerebral artery occlusion (MCAO).3 Reperfusion/reoxygenation after an ischemic episode can significantly exacerbate injury to the brain, as demonstrated in a rodent model of focal permanent and transient cerebral ischemia.4 In the present study we tested the hypothesis that chronic treatment with lithium at a low dose improves the recovery from transient focal cerebral ischemia and reduces infarct volume. Lithium has a narrow therapeutic window. Therefore, even small increases in its serum concentrations may induce serious adverse sequelae.5 In rodents, the ischemic area induced by MCAO can be divided into an ischemic core and the penumbra. In the core region, necrotic cell death occurs rapidly, whereas in the penumbral area neuronal damage develops more slowly.6 Among the factors contributing to delayed injury, progression in the penumbra, apoptosis, and inflammation play key roles.7,8 Although lithium can protect the brain after stroke, the mechanisms responsible for its neuroprotective effects remain unclear. In the present study we examined the effect of lithium on apoptosis markers (activated caspase-3 immunoreactivity and subsequent DNA fragmentation). Staining for activated microglia helped to assess ongoing inflammatory processes in the ischemic brain. The expression of activator protein 1 (AP-1) as an indicator of neuronal damage was also studied.

Materials and Methods
Male normotensive Wistar rats (body weight, 200 to 230 g) were obtained from Charles River (Sulzfeld, Germany). All rats were housed at constant humidity and temperature with a 12-hour light/dark cycle and free access to food and water.
Unilateral MCAO With Reperfusion

We used an intraluminal occlusion method with subsequent reperfusion.\(^9\) Rats were anesthetized with chloral hydrate (400 mg/kg body wt IP); a silicone-coated 4-0 nylon monofilament was advanced through the right common carotid artery and the internal carotid artery up to 17 mm from the bifurcation of the common carotid artery and the external carotid artery. Cerebral blood flow (CBF) was monitored by laser-Doppler flowmetry. Reperfusion began 90 minutes after MCAO. Rectal temperature was monitored and maintained between 37.0°C and 37.5°C with a heating pad.

Measurement of Blood Pressure and Blood Parameters

Mean arterial blood pressure was measured with a catheter inserted into the femoral artery from 2 hours after the last lithium or vehicle treatment up to 90 minutes after the onset of reperfusion.

Blood parameters (pH, P\(_{\text{CO}_2}\), P\(_{\text{O}_2}\), plasma concentrations of glucose, lactate, potassium, sodium, and chloride) were quantified with the use of Radiometer ABL 700 Series at the following time points: 2 hours after treatment (conscious rats); 10 minutes after the initiation of anesthesia before MCAO; 30 and 90 minutes after MCAO; and 30 minutes after the onset of reperfusion.

Measurement of Regional CBF

Regional CBF (rCBF) was monitored continuously before, during, and after MCAO in the cerebral cortex of each hemisphere in the supply territory of the MCA by a laser-Doppler flowmeter (Periflux system 5000).\(^{10}\)

Drug Administration and Experimental Design

Two groups of rats were treated daily by a subcutaneous injection with LiCl (1 mmol/kg; n=10) or vehicle (0.9% NaCl; n=11) for 2 weeks. Two hours after the last drug application, rats underwent MCAO for 90 minutes followed by reperfusion. Drug treatment was continued for another 2 days after MCAO. Neurological evaluation was performed in all rats 2 hours after drug treatment on days 1 and 2 after MCAO. Two days after MCAO, blood was collected for the measurement of lithium concentration by a flame photometer (Eppendorf EFOX 5053). Brains were used for the measurement of infarct volume and immunohistochemical examinations. Cardiovascular and blood parameters were evaluated in a separate experiment.

Evaluation of Neurological Deficits

The neurologic status of each rat was evaluated 24 and 48 hours after MCAO by a blinded observer. Two neurological grading systems were used: (1) a grading scale of 0 to 3 developed by Bederson et al\(^{11}\) and (2) a grading scale of 3 to 18 developed by Garcia et al.\(^{12}\)

Tissue Processing

Two days after MCAO, rats were anesthetized and intracardially perfused with PBS followed by 4% paraformaldehyde. The brains were removed, and coronal sections (40 μm) were cut from bregma +3.7 mm to bregma –6.7 mm on a cryostat. Every 20th slice was used for the measurement of infarct size. Consecutive slices from different brain areas (bregma –0.3 and –1.8 mm) were used for the staining of terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL), caspase-3, activated microglia, and c-Jun/c-Fos.

Measurement of Infarct Volume

The sections stained with cresyl violet were analyzed at 14 levels. Slice images were digitalized, the area of infarction was measured by the use of the formula of Swanson et al.\(^{15}\) The percentage of hemisphere suffering infarction was then calculated with the use of the contralateral and ipsilateral hemisphere areas were measured, and the difference between both areas in each section was used to calculate the edema volume.\(^{14}\) The percentage of hemisphere suffering infarction was then calculated with the use of the formula of Swanson et al.\(^{15}\)

Immunohistochemical Detection of Apoptosis and Inflammation

Immunohistochemical staining was performed at bregma –0.3 and –1.8 mm. The slices were grouped into 5 sets. The first set was stained with TUNEL as described in the manufacturers’ protocol (Roche). The second set was stained for caspase-3: the brain sections were incubated with a primary antibody against caspase-3 (cleaved caspase-3 antibody, 17 kDa, Cell Signaling, dilution 1:100) overnight at 4°C and visualized with a Vectastain ABC kit (Vector) and 3’,3’-diaminobenzidine (Sigma) as chromogen, as described before.\(^{16}\) The third, fourth, and fifth sets were stained for activated microglia/macrophages, c-Fos, and c-Jun, respectively. The brain sections were incubated with the primary antibody (mouse anti-rat ED1, Serotec, dilution 1:300; anti-c-Fos antiserum, Oncogene, dilution 1:300; anti-c-Jun antiserum, Oncogene, dilution 1:300) for 2 nights at 4°C. The following procedure was the same as for caspase-3 staining. A total of 6 rats were used for each staining in either group. Positive cells were counted with the use of a computer program (Leica QWin). Three random and nonoverlapping regions (375×500 μm) were sampled at the cortical border of the positively stained area (Figure 1A). For TUNEL-labeled cells, only densely stained cells were considered as positive apoptotic cells, and cells with light diffuse labeling suggesting necrosis were not counted (Figure 1B).

Statistical Analysis

All data are expressed as mean±SEM. Comparisons were performed by the Kruskal-Wallis test. Values of P<0.05 were considered statistically significant.

Results

Blood Pressure and Blood Parameters

No significant differences in mean arterial blood pressure before MCAO, during MCAO, and after reperfusion were...
determined between LiCl-treated rats and vehicle-treated rats (data not shown). The values of pH, PCO₂, PO₂, and blood concentrations of glucose, lactate, and the electrolytes Na⁺, K⁺, and Cl⁻ were not significantly different between the LiCl-treated group and the vehicle-treated group at any time point (Table).

**Neurological Evaluation**

Rats treated with LiCl showed a significantly improved neurological outcome compared with rats treated with vehicle at days 1 and 2 after MCAO. The difference in the neurological outcome between vehicle-treated and lithium-treated rats was evident with both the grading scale of 0 to 3 developed by Bederson et al and the grading scale of 3 to 18 developed by Garcia et al (Figure 2).

**Cerebral Blood Flow**

CBF reductions during MCAO and posts ischemic reperfusion values were identical between the vehicle- and LiCl-treated groups (Figure 3C). Only rats with a reduction of CBF of ≥80% were included in the study. Contralateral CBF fluctuated at approximately 100% of baseline. After withdrawal of the filament, ipsilateral CBF was restored to approximately 60% of baseline in both vehicle- and LiCl-treated rats (Figure 3C).

**Infarct Volume and Edema Volume**

LiCl treatment significantly reduced the total infarct volume by 32.7% compared with the vehicle group (Figure 3A). The percentage of infarction, corrected for cerebral edema, was

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**Table 1: Physiological Parameters in Rats Treated With LiCl Before, During, and After 90-Minute MCAO**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle (n=7)</th>
<th>LiCl (n=7)</th>
<th>Vehicle (n=7)</th>
<th>LiCl (n=7)</th>
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<tbody>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conscious</td>
<td>7.43±0.01</td>
<td>7.41±0.01</td>
<td>34.4±1.1</td>
<td>35.6±1.4</td>
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<td>Anesthesia</td>
<td>7.33±0.02</td>
<td>7.30±0.01</td>
<td>47.5±1.3</td>
<td>50.1±2.8</td>
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<td>30-min MCAO</td>
<td>7.38±0.03</td>
<td>7.37±0.02</td>
<td>44.8±2.6</td>
<td>43.4±2.7</td>
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<tr>
<td>90-min MCAO</td>
<td>7.42±0.02</td>
<td>7.40±0.03</td>
<td>37.5±1.1</td>
<td>37.2±2.8</td>
</tr>
<tr>
<td>30-min reperfusion</td>
<td>7.37±0.01</td>
<td>7.36±0.02</td>
<td>40.5±1.3</td>
<td>40.4±2.1</td>
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<tr>
<th>PO₂ mm Hg</th>
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<tr>
<td>Conscious</td>
<td>80.4±2.8</td>
<td>80.1±1.1</td>
<td>123.4±11.0</td>
<td>115.0±5.0</td>
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<tr>
<td>Anesthesia</td>
<td>72.7±2.4</td>
<td>71.2±2.7</td>
<td>178.9±10.0</td>
<td>171.4±8.1</td>
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<tr>
<td>30-min MCAO</td>
<td>73.8±2.5</td>
<td>80.5±3.2</td>
<td>187.9±12.4</td>
<td>169.6±12.5</td>
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<tr>
<td>90-min MCAO</td>
<td>78.9±3.2</td>
<td>83.1±1.9</td>
<td>186.5±12.9</td>
<td>162.4±14.7</td>
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<tr>
<td>30-min reperfusion</td>
<td>83.4±2.6</td>
<td>84.1±2.4</td>
<td>194.1±14.9</td>
<td>189.8±19.5</td>
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<table>
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<tr>
<th>lLac mmol/L</th>
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<tr>
<td>Conscious</td>
<td>1.59±0.16</td>
<td>1.54±0.13</td>
<td>111.0±1.6</td>
<td>109.1±1.3</td>
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<tr>
<td>Anesthesia</td>
<td>3.51±0.29</td>
<td>3.27±0.34</td>
<td>106.5±0.8</td>
<td>103.9±1.3</td>
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<tr>
<td>30-min MCAO</td>
<td>2.10±0.18</td>
<td>2.17±0.18</td>
<td>104.9±0.8</td>
<td>103.3±1.2</td>
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<tr>
<td>90-min MCAO</td>
<td>2.10±0.19</td>
<td>2.01±0.16</td>
<td>106.0±0.9</td>
<td>104.4±1.1</td>
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<td>30-min reperfusion</td>
<td>1.85±0.17</td>
<td>1.70±0.12</td>
<td>106.8±0.7</td>
<td>103.8±1.1</td>
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<table>
<thead>
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<th>cNa⁺ mmol/L</th>
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<tbody>
<tr>
<td>Conscious</td>
<td>142.4±0.7</td>
<td>140.2±0.6</td>
<td>3.61±0.14</td>
<td>3.71±0.21</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>137.9±0.8</td>
<td>135.4±0.8</td>
<td>4.47±0.09</td>
<td>4.59±0.24</td>
</tr>
<tr>
<td>30-min MCAO</td>
<td>136.7±0.8</td>
<td>133.9±1.0</td>
<td>4.21±0.13</td>
<td>4.43±0.23</td>
</tr>
<tr>
<td>90-min MCAO</td>
<td>135.8±1.1</td>
<td>133.8±1.4</td>
<td>4.39±0.10</td>
<td>4.36±0.24</td>
</tr>
<tr>
<td>30-min reperfusion</td>
<td>135.5±0.8</td>
<td>131.9±0.6</td>
<td>3.64±0.20</td>
<td>3.96±0.15</td>
</tr>
</tbody>
</table>

Data are mean±SEM of the number of rats. cGlu, cLac, cNa⁺, cK⁺, and cCl⁻ indicate plasma concentration of glucose, lactate, Na⁺, K⁺, and Cl⁻.

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**Figure 2.** Effect of chronic treatment with LiCl on neurological deficit scores assessed by 2 different grading evaluation systems: 0 to 3 (A) and 3 to 18 (B). Data are expressed as mean±SEM; *P<0.05, **P<0.01 vs vehicle-treated animals.
significantly reduced in the LiCl-treated group compared with the vehicle-treated group (Figure 3B). LiCl treatment slightly but not significantly reduced edema volume (vehicle group, 73.8 ± 11.8 mm³; lithium group, 55.1 ± 8.7 mm³).

**TUNEL Staining**

TUNEL-positive cells were distributed in the boundary zones (penumbras) and ischemic cores of the cerebral cortex and caudate putamen of the occluded MCA area. The sections through the anterior commissure (0.3 mm posterior to the bregma) revealed significantly fewer TUNEL-positive cells in rats treated with LiCl than in those treated with vehicle (473 ± 60.7/mm² versus 805 ± 60.5/mm²; \( P < 0.01 \); 41.2% reduction). A 30.3% reduction in the number of TUNEL-positive cells was also observed on the sections ±1.8 mm from bregma (lithium, 606 ± 83.1/mm²; vehicle, 870 ± 72.5/mm²; \( P < 0.05 \)) (Figures 4A, 5A, and 5B). No TUNEL-positive cells were found on the contralateral side.

**Activated Caspase-3 Immunoreactivity**

The majority of caspase-3-positive cells were distributed in the inner boundary zones (penumbras) of the cerebral cortex and caudate putamen of the occluded MCA area. On the other hand, only a few cells positively stained for caspase-3 were found in the ischemic core region. Animals treated with LiCl exhibited significantly fewer caspase-3-positive cells in the penumbral zone of the parietal cortex in the section through the anterior commissure than those treated with vehicle (215 ± 35.1/mm² versus 386 ± 45.7/mm²; \( P < 0.01 \); 44.3% reduction). At 1.8 mm posterior to the bregma, the number of
caspase-3–positive cells was reduced by 32.2% in sections from LiCl-treated rats (lithium, 289 ± 57.3/mm²; vehicle, 426 ± 45.3/mm²) (Figures 4B, 5C, and 5D). A negligible amount of caspase-3–positive cells were found in the cortical area of the contralateral side.

Activated Microglia
Activated microglial cells of the amoeboid type (amoeboid microglia), identified by their enlarged size and stout processes, were most frequently observed in the boundary zone of the infarction and to a minor extent in the infarction core 2 days after MCAO. The density of activated microglial cells and macrophages in the penumbra of the parietal cortex on the sections 0.3 and 1.8 mm posterior to bregma did not differ between the 2 groups (Figures 4C, 5E, and 5F). No activated microglia and macrophages were found on the contralateral side.

AP-1 Protein Expression
C-Jun expression in the penumbra of the ischemic cortex was significantly reduced in the lithium-treated animals compared with the vehicle-treated rats (210 ± 19.9/mm² versus 321 ± 33.9/mm²; P < 0.05) (Figure 4D). C-Fos expression was very low 2 days after MCAO in both groups and was therefore not evaluated.

Plasma Lithium Concentration
Daily subcutaneous injection of LiCl (1 mmol/kg) for 16 days yielded a plasma Li⁺ concentration of 0.40 ± 0.06 mmol/L (n = 6).

Discussion
The first important finding of the present study is that chronic treatment with a low dose of lithium decreased infarct volume and improved neurological outcome. Similar findings were obtained by Nonaka and Chuang in rats with permanent MCAO after chronic treatment with lithium. In their study rats were treated with lithium (initially 1.5 mmol/kg, then 2.3 mmol/kg, and finally 3 mmol/kg) for 16 days, and neurological evaluation or quantification of infarct volume was performed at 24 hours after MCAO. Both studies differ with respect to the model used (transient versus permanent MCAO), the dose of lithium (1 versus 3 mmol/kg), and the time point (48 versus 24 hours after MCAO). Furthermore, in the study by Nonaka and Chuang, no attempt was made to examine the possible mechanisms that may be responsible for the lithium-induced neuroprotection. In the present study the neuroprotective effects of lithium were associated with a reduction of apoptotic events in the brain cortex assessed by 2 different methods. The results clearly demonstrate that chronic treatment with lithium (1 mmol/kg) inhibits activated caspase-3 expression and decreases DNA fragmentation in the brain after transient focal cerebral ischemia. The apoptotic parameters were evaluated 2 days after MCAO because (1) pannecrosis is visible 24 to 48 hours after MCAO and (2) the number of apoptotic cells, mostly neurons, increases as early as 0.5 hours, peaks at 24 to 48 hours, and persists for 4 weeks after the onset of reperfusion. Furthermore, apoptotic cells were located primarily in the inner boundary zone of the infarct of rats subjected to transient (2-hour) focal ischemia.

Ischemia is known to produce reactive oxygen and nitrogen species and to induce cleavage of poly(ADP-ribose) polymerase, caspase activation, and DNA fragmentation in neuronal cells. In particular, recent biochemical and immunohistochemical studies have demonstrated enhanced expression and activation of intracellular proteases, notably caspase-3, which act as initiators and executors of the apoptotic process. The involvement of caspases in apoptotic processes after ischemia is supported by the observation that treatment with caspase inhibitors reduces ischemia-induced brain damage. These data suggest that apoptotic mechanisms are activated during ischemia and that inhibition of apoptosis reduces ischemic brain damage. The gradual expansion of the ischemic lesion after MCAO has been visualized in the parietal cortex by microtubule-associated protein 2 immunostaining. Therefore, we used the penumbra of the parietal cortex to measure the density of apoptotic and inflammatory cells to assess the possible therapeutic effects of lithium on apoptotic and inflammatory processes. Our results demonstrate that lithium significantly inhibited activated caspase-3 immunoreactivity and decreased DNA fragmentation in the ischemic penumbra of the brain cortex 48 hours after MCAO. Several studies have demonstrated anti-apoptotic effects of lithium. Chronic treatment with lithium increased the expression of Bcl-2, an anti-apoptotic protein, both in vitro and in vivo and reduced the levels of the pro-apoptotic proteins p53 and Bax. These data support the hypothesis that the lithium-mediated protection from cerebral ischemia involves anti-apoptotic mechanisms. Cerebral ischemia induces an exaggerated inflammatory response in the surroundings of the cerebral infarct that might contribute to neuronal necrosis and apoptosis due to the release of cytokines and other neurotoxic factors. A significant number of reactive mononuclear phagocytes, both microglia and invading macrophages, appear within the infarct area and along neighboring marginal areas 2 days after ischemia. In the present study we investigated activated microglia as a parameter for ongoing inflammatory processes 48 hours after MCAO. Lithium did not inhibit activated microglia in the ischemic penumbra of the brain cortex. Therefore, it seems likely that anti-apoptotic rather than anti-inflammatory effects of lithium had contributed to its neuroprotective effects.

Numerous studies have shown that lithium must be chronically administered to reach therapeutic effects. Furthermore, it has been postulated that lithium may exert major effects at the genomic level. Recently, lithium has been demonstrated to inhibit glycogen synthase kinase-3β (GSK-3β), an enzyme that is involved in pro-apoptotic signaling. Therefore, the neuroprotective actions of lithium may be partly due to inhibition of GSK-3β.

Cerebral ischemia dramatically increased the expression of c-Jun and c-Fos in the ipsilateral cortex. In general, AP-1 proteins were stimulated in cortical regions that survive the ischemic insult. Lithium has been reported to modulate the AP-1 DNA binding activity and the expression of genes regulated by AP-1. Our finding that lithium treatment reduces the expression of c-Jun 2 days after MCAO may indicate an
involvement of AP-1 proteins in the neuroprotective effects of the substance. We have shown previously that the expression of both c-Jun and c-Fos is elevated 24 hours after MCAO. In the present study the expression of c-Fos was weak compared with that of c-Jun. Differences in the time courses of c-Jun and c-Fos expression have also been observed in other experimental paradigms, e.g., after stimulation of periventricular AT-1 receptors. C-Fos expression was strongly upregulated at early time points but returned to basal values much faster than c-Jun.26

In the present study the plasma Li+ concentration in Wistar rats after 16 days of treatment reached values of 0.40 ± 0.06 mmol/L. This concentration is below the therapeutic concentrations of lithium (0.5 to 0.9 mmol/L) required in humans for the treatment of manic depression.27 In vitro therapeutic concentrations of lithium (0.5 to 0.9 mmol/L) required /H11006 0.06 mmol/L. This concentration is below the therapeutic effects of lithium against ischemic brain injury.

The process is most probably responsible for the neuroprotective effects of both c-Jun and c-Fos is elevated 24 hours after MCAO.25 In the present study the expression of c-Fos was strongly upregulated at early time points but returned to basal values much faster than c-Jun.26

In the present study the plasma Li+ concentration in Wistar rats after 16 days of treatment reached values of 0.40 ± 0.06 mmol/L. This concentration is below the therapeutic concentrations of lithium (0.5 to 0.9 mmol/L) required in humans for the treatment of manic depression.27 In vitro study showed that pretreatment of cortical neurons with LiCl suppressed glutamate-induced excitotoxicity at the therapeutic and subtherapeutic concentration of 0.2 to 1.6 mmol/L, with almost complete protection at 1 mmol/L.28 In the present study a low dose of lithium reduced the infarct volume by 32.7%. A more pronounced effect of lithium can be expected at higher doses, as demonstrated by Nonaka and Chuan.3

In conclusion, we demonstrated that a low-dose treatment with lithium (1 mmol/kg) reduced infarct volume and improved neurological outcome in rats with transient focal cerebral ischemia. Lithium showed a significant reduction in the AP-1 transcription factor c-Jun and an inhibition of caspase-3 and DNA fragmentation in the ischemic penumbra of the brain cortex, indicating that a reduction of apoptotic processes is most probably responsible for the neuroprotective effects of lithium against ischemic brain injury.

References


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