Increased Extracellular K\(^+\) Concentration Reduces the Efficacy of N-methyl-D-aspartate Receptor Antagonists to Block Spreading Depression-Like Depolarizations and Spreading Ischemia

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**Background and Purpose**—Spreading depression (SD)-like depolarizations may augment neuronal damage in neurovascular disorders such as stroke and traumatic brain injury. Spreading ischemia (SI), a particularly malignant variant of SD-like depolarization, is characterized by inverse coupling between the spreading depolarization wave and cerebral blood flow. SI has been implicated in particular in the pathophysiology of subarachnoid hemorrhage. Under physiological conditions, SD is blocked by N-methyl-D-aspartate receptor (NMDAR) antagonists. However, because both SD-like depolarizations and SI occur in presence of an increased extracellular K\(^+\) concentration ([K\(^+\)]\(_o\)), we tested whether this increase in baseline [K\(^+\)]\(_o\) would reduce the efficacy of NMDAR antagonists.

**Methods**—Cranial window preparations, laser Doppler flowmetry, and K\(^+\)-sensitive/reference microelectrodes were used to record SD, SD-like depolarizations, and SI in rats in vivo; microelectrodes and intrinsic optical signal measurements were used to record SD and SD-like depolarizations in human and rat brain slices.

**Results**—In vivo, the noncompetitive NMDAR antagonist dizocilpine (MK-801) blocked SD propagation under physiological conditions, but did not block SD-like depolarizations or SI under high baseline [K\(^+\)]\(_o\). Similar results were found in human and rat neocortical slices with both MK-801 and the competitive NMDAR antagonist D-2-amino-5-phosphonovaleric acid.

**Conclusions**—Our data suggest that elevated baseline [K\(^+\)]\(_o\) reduces the efficacy of NMDAR antagonists on SD-like depolarizations and SI. In conditions of moderate energy depletion, as in the ischemic penumbra, or after subarachnoid hemorrhage, NMDAR inhibition may not be sufficient to block these depolarizations. (*Stroke*. 2005;36:1270-1277.)

**Key Words:** brain injuries | N-methyl-D-aspartate | spreading cortical depression | subarachnoid hemorrhage

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Spreading depression (SD) is a slowly propagating neuroglial depolarization wave\(^1\) that is not deleterious to neuronal tissue.\(^2\) In contrast, in the ischemic penumbra, SD-like depolarizations occur\(^3^,^4\) that are preceded by a gradual increase of the extracellular K\(^+\) concentration ([K\(^+\)]\(_o\))\(^5^,^6\) and may augment neuronal damage.\(^7\) If, in addition to elevated [K\(^+\)]\(_o\), the nitric oxide concentration is reduced, SD-like depolarizations induce ischemic blood flow changes that propagate with the depolarization wave (spreading ischemia [SI]).\(^8^,^9\) It has been proposed that SI may underlie the laminar cortical infarcts that represent the predominant infarct pattern in autopsy studies after subarachnoid hemorrhage (SAH), because SI: (1) induces focal cortical parenchymal necrosis\(^10^,^11\); (2) can be triggered by products of erythrocytolyis\(^8\); and (3) is prevented by drugs clinically used for the prophylaxis of infarcts after SAH.\(^12\)

N-methyl-D-aspartate receptor (NMDAR) antagonists have been regarded promising candidates to inhibit SD-like depolarizations and SI, because they block SD under physiological conditions.\(^13^,^14\) However, their efficacy seems to be reduced under energy depletion.\(^15^,^16^,^17\) Here, we have studied whether elevated baseline [K\(^+\)]\(_o\) may be the cause of this reduced drug efficacy.
TABLE 1. Physiological Variables

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP, mm Hg</th>
<th>PaCO₂, mm Hg</th>
<th>PaO₂, mm Hg</th>
<th>pH</th>
<th>BT, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>113±17</td>
<td>39.2±4.4</td>
<td>117.6±9.3</td>
<td>7.43±0.04</td>
<td>37.4±0.4</td>
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<tr>
<td>2</td>
<td>136±15</td>
<td>42.5±2.7</td>
<td>120.1±9.8</td>
<td>7.38±0.02</td>
<td>36.8±0.2</td>
</tr>
<tr>
<td>3</td>
<td>137±32</td>
<td>41.3±1.9</td>
<td>122.3±16.6</td>
<td>7.39±0.02</td>
<td>36.7±0.2</td>
</tr>
<tr>
<td>4</td>
<td>128±22</td>
<td>42.3±2.2</td>
<td>117.7±13.6</td>
<td>7.39±0.02</td>
<td>36.7±0.2</td>
</tr>
</tbody>
</table>

BT indicates body temperature; MAP, mean arterial blood pressure; PaCO₂, arterial CO₂ pressure; PaO₂, arterial O₂ pressure.

Materials and Methods

Chemicals were purchased from Sigma-Aldrich unless otherwise stated. All experiments conformed to institutional guidelines and were approved by an official committee.

In Vivo Experiments

Male Wistar rats (250 to 450 grams; Charles River Laboratories, Wilmington, Mass.) were anesthetized with 100 mg/kg thiopental (BYK-Chemie) intraperitoneally, tracheotomized, and ventilated (Rodenst:Respirator; Effenberger). Saline solution was infused through the femoral artery. Mean arterial pressure, PaO₂, PaCO₂, and pH were monitored. Body temperature was maintained at 38.0±0.5°C. After craniotomy and dura removal, a single cranial window was implanted in groups 1 to 3, and 2 windows in group 4.

The cortex was continuously superfused with carbogenated artificial cerebrospinal fluid (ACSF) containing (mmol) 152 Na⁺, 3 K⁺, 1.5 Ca²⁺, 1.2 Mg²⁺, 24.5 HCO₃⁻, 135 Cl⁻, 3.7 glucose, and 6.7 urea. Cerebral blood flow was monitored with 2 laser Doppler probes (Perimed, Järfälla, Sweden). Intracortical extracellular [K⁺], and steady (direct current [DC]) potential were measured with 2 K⁺-selective/reference microelectrodes (300 μm depth). Subarachnoid DC potential and electrocorticogram were recorded by an AgCl electrode. The parameters were recorded using a chart recorder (DASH-IV; Astro-Med). Absolute DC potential and [K⁺] changes were analyzed; cerebral blood flow changes were calculated in relation to baseline at the onset of experiments (100%; zero levels were established at the end of experiments after global ischemia).

Brain Slices and Measurement of SD

Wistar rats (150 to 200 grams) were decapitated under ether anesthesia. Coronal neocortical slices (400 μm) were obtained using a vibratome (WPI) and perfused with prewarmed carbogenated ACSF containing (mmol) 126 NaCl, 3 KCl, 2 MgSO₄, 2 CaCl₂, 10 glucose, 1.25 NaHPO₄, and 26 NaHCO₃ (pH 7.4) in a interfase-type chamber. Human neocortical tissue was obtained from patients undergoing surgery for pharmacoresistant epilepsy. The study was conducted according to the Declaration of Helsinki and approved by the local ethics committee (patients gave written informed consent). Slices (400 μm) were prepared as described.

DC potential amplitude, duration at half-maximal amplitude (Tmax), and [K⁺]₀, were recorded by 2 K⁺-selective/reference microelectrodes in layers II/III and digitized with a DASH-8u recorder (Astro-Med). Intrinsic optical signals were monitored by transilluminating slices and recorded using a microscope-mounted CCD camera. The control image in a series, captured before SD, was subtracted from each subsequent image, revealing changes in light transmittance (LT) over time. Regions of interest were selected to quantify and compare LT changes. SD velocity was determined by the propagation of the transient LT decrease.

Results

The systemic variables of the in vivo experiments remained within physiological limits (Table 1). The experimental data are summarized in Tables 2 and 3.

NMDAR Blockade Does not Inhibit SI

In group 1, we generated SI by continuously applying the nitric oxide scavenger hemoglobin (2.5 mmol/L) and increasing [K⁺]₀ in an ACSF in a stepwise manner (3, 25, 35 mmol/L) (n=6). [K⁺]₀, gradually increased before SI (caudal microelectrode, 6.7±1.0 mmol/L; rostral microelectrode, 9.1±4.4 mmol/L).

TABLE 2. In Vivo Experiments

<table>
<thead>
<tr>
<th>Probe/Window</th>
<th>CBFhyper, %</th>
<th>CBFhyper Duration, sec</th>
<th>CBFhyper</th>
<th>CBF Delay, s</th>
<th>DC Amp, mV</th>
<th>DC Delay, sec</th>
<th>Pre-SD [K⁺]₀, mmol</th>
<th>SD [K⁺]₀, mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (SI, 1 window) Control</td>
<td>43±8</td>
<td>624±681</td>
<td>248±121</td>
<td>42±33</td>
<td>20.5±6.9</td>
<td>47±38</td>
<td>6.7±1.0</td>
<td>32.1±7.0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-21.6±7.4</td>
<td>9.1±4.4</td>
<td>42.6±11.7</td>
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</tr>
<tr>
<td>Group 2 (SI, 1 window) MK-801 Control</td>
<td>31±18</td>
<td>686±718</td>
<td>188±92</td>
<td>36±21</td>
<td>16.3±3.4</td>
<td>38±23</td>
<td>8.6±2.8</td>
<td>29.1±15.6</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>-23.1±3.9</td>
<td>12.6±1.9</td>
<td>52.3±22.1</td>
<td></td>
</tr>
<tr>
<td>Group 3 (SDLD, 1 window) Control</td>
<td>95±16</td>
<td>12±7</td>
<td>236±119</td>
<td>43±18</td>
<td>15.8±1.9</td>
<td>59±20</td>
<td>7.7±6.8</td>
<td>48.1±12.3</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>-15.9±5.5</td>
<td>5.7±5.8</td>
<td>49.5±14.4</td>
<td></td>
</tr>
<tr>
<td>Group 4 (SDLD/SD, 2 windows) Control</td>
<td>133±28</td>
<td>19±14</td>
<td>315±68</td>
<td>53±21</td>
<td>12.6±1.8</td>
<td>45±15</td>
<td>15.6±4.9</td>
<td>54.4±13.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-14.7±1.8</td>
<td>11.3±4.7</td>
<td>36.3±15.9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-17.8±2.6</td>
<td>10.9±15*</td>
<td>56.8±8.4</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.7±3.7</td>
<td>3.0±0.3*</td>
<td>44.8±12.8</td>
<td></td>
</tr>
</tbody>
</table>

Data are given for spreading ischemia (SI, groups 1 and 2), SD-like depolarizations (SDLD) and spreading depression (SD; groups 3 and 4). In groups 1 to 3, one cranial window was superfused and data are given for the caudal and rostral probes. In group 4, data are given for 2 separately superfused windows. SI was generated in absence (group 1) and presence (group 2) of MK-801. In groups 3 and 4, data are given for depolarizations before and after the administration of MK-801.

CBFhyper indicates lowest cerebral blood flow level during initial hyperperfusion; CBFhyper Duration, duration of CBFhyper; CBFhyper highest CBF level during transient hyperemia; CBF Delay, delay of onset of CBFhyper between laser Doppler probes; DC Amp, amplitude of DC shift during depolarization; DC Delay, delay of onset of DC shift between microelectrodes; Pre-SD [K⁺]₀, tissue K⁺ concentration before depolarization onset; SD [K⁺]₀, highest K⁺ concentration during depolarization.

Group 1 was compared with group 2, and group 3 was compared with group 4 using Student t test, paired t test, and Mann–Whitney rank-sum test when necessary (*P<0.05).
SI was characterized by a long-lasting cerebral blood flow decrease to ischemic levels, followed by a transient hyperemia (Table 2 and Figure 1A). These flow changes were accompanied by a transient negativation of the DC potential and a transient peak of $[K^+]_o$. The delay between the onset of the hypoperfusion at the 2 laser probes indicated a propagation of the ischemic flow changes. This group was compared with group 2 (n = 6) in which SI was generated by the same protocol, but the noncompetitive NMDAR antagonist MK-801 (5 mg/kg) was bolus-injected twice intravenously: at normal and at elevated $[K^+]_o$.

We superfused the cortex with high $[K^+]_o$ (130 mmol/L) to generate SD-like depolarizations, and these depolarizations were then recorded as SDs at the rostral window superfused with physiological ACSF throughout the experiments. High $[K^+]_o$ at the caudal window caused a gradual increase in $[K^+]_o$, (6.7 ± 3.7 mmol/L), whereas $[K^+]_o$ remained constant rostrally; 5 ± 4 SD-like depolarizations occurred at the caudal window, and 3 ± 1 of these depolarizations propagated to the rostral window. After MK-801 administration, SD-like depolarizations still occurred at the caudal window (8 ± 2/60 minutes), but propagation into the rostral window was completely blocked. Figure 2 illustrates an example.

### NMDAR Blockade Does Not Inhibit SD-Like Depolarizations at High $[K^+]_o$

We superfused the cortex with high $[K^+]_{ACSF}$ (130 mmol/L) to generate SD-like depolarizations in vivo (n = 5; lower $[K^+]_{ACSF}$ does not reliably induce SD-like depolarizations in vivo). The microelectrodes and laser probes were positioned at opposite ends of a single cranial window. Before the SD-like depolarizations, $[K^+]_o$ increased to 7.7 ± 6.8 mmol/L (caudally) and 5.7 ± 5.8 mmol/L (rostrally). SD-like depolarizations occurred in all animals, characterized by a negative DC shift, a transient $[K^+]_o$ increase, and a short hypoperfusion and transient hyperemia as described. There was a delay between the recording sites at the window, indicating a propagation of the neurovascular changes (Figure 1B). Compared with SI (groups 1 to 2), the DC shift duration and the extent and duration of the hypoperfusion were significantly smaller ($P<0.001$, Student t test). After 3 SD-like depolarizations had been recorded, the perfusion was switched to physiological ACSF and MK-801 was bolus-injected. When MK-801 had reached the cerebral tissue, we again increased $[K^+]_{ACSF}$. This induced repetitive SD-like depolarizations in all animals with no differences to SD-like depolarizations without MK-801, but at a significantly higher $K^+$ threshold (15.6 ± 4.9 mmol/L caudally, 11.3 ± 4.7 mmol/L rostrally). Thus, NMDAR blockade shifted the threshold, but it did not block SD-like depolarizations at high $[K^+]_o$.

### NMDAR Blockade Prevents SD Propagation From Tissue With Elevated $[K^+]_o$ Into Tissue With Normal $[K^+]_o$

We implanted 2 ipsilateral cranial windows to investigate the susceptibility of SD-like depolarizations and SD to MK-801 (n = 5). The caudal window was superfused with high $[K^+]_{ACSF}$ (130 mmol/L) to generate SD-like depolarizations, and these depolarizations were then recorded as SDs at the rostral window superfused with physiological ACSF throughout the experiments. High $[K^+]_{ACSF}$ at the caudal window caused a gradual increase in $[K^+]_o$, (6.7 ± 3.7 mmol/L), whereas $[K^+]_o$ remained constant rostrally; 5 ± 4 SD-like depolarizations occurred at the caudal window, and 3 ± 1 of these depolarizations propagated to the rostral window. After MK-801 administration, SD-like depolarizations still occurred at the caudal window (8 ± 2/60 minutes), but propagation into the rostral window was completely blocked. Figure 2 illustrates an example.

### NMDAR Blockade Blocks SD Under Normal in Contrast to High $[K^+]_o$, in Rat Brain Slices

We tested whether NMDAR antagonists shift the threshold for SD-like depolarizations evoked by high $[K^+]_o$. We increased $[K^+]_{ACSF}$ in a stepwise manner (2.5 mmol/L/60 minutes) in rat neocortical slices perfused with the competitive NMDAR antagonist 2-APV (n = 6). The first SD-like depolarization occurred when $[K^+]_o$ reached 12.3 ± 1.7 mmol/L, characterized by a negative DC shift and a transient increase of $K^+$. Optical changes consisted of a sudden LT decrease simultaneously with the DC shift. Occasionally, depolarizations initiated at several foci at approximately the same time. After post-SD recovery, slices were perfused with 2-APV (30 μmol/L) under continuously elevated $[K^+]_{ACSF}$. No SD-like depolarization occurred under this condition, whereas SD-like depolarizations were detected at the same $[K^+]_{ACSF}$ in control slices of the contralateral hemisphere. Subsequently, $[K^+]_{ACSF}$ was further raised by 5 mmol/L during continuous perfusion with 2-APV, inducing SD-like depolarizations in all.

### Table 3. Brain Slice Experiments

<table>
<thead>
<tr>
<th>Group</th>
<th>NMDAR Blockade</th>
<th>DC Amp, mV</th>
<th>DC T$_{max}$, sec</th>
<th>Pre-SD $[K^+]_o$, mmol/L</th>
<th>SD $[K^+]_o$, mmol/L</th>
<th>SD$_{des}$ mm/min</th>
<th>LT Decrease, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (rat)</td>
<td>...</td>
<td>−11.9 ± 4.9</td>
<td>71 ± 36</td>
<td>12.3 ± 1.7</td>
<td>36.4 ± 14.7</td>
<td>4.1 ± 0.8</td>
<td>−10.6 ± 3.2</td>
</tr>
<tr>
<td>2-APV</td>
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<tr>
<td>6 (rat)</td>
<td>...</td>
<td>−16.3 ± 4.3</td>
<td>63 ± 21</td>
<td>11.6 ± 3.1</td>
<td>46.9 ± 9.2</td>
<td>4.0 ± 0.9</td>
<td>−9.9 ± 2.8</td>
</tr>
<tr>
<td>MK-801</td>
<td></td>
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</tr>
<tr>
<td>7 (rat)</td>
<td>...</td>
<td>−11.7 ± 4.2</td>
<td>32 ± 9*</td>
<td>3.2 ± 0.3</td>
<td>44.8 ± 14.6</td>
<td>3.4 ± 0.8</td>
<td>−9.1 ± 1.4</td>
</tr>
<tr>
<td>MK-801</td>
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</tr>
<tr>
<td>8 (rat)</td>
<td>...</td>
<td>−9.8 ± 4.9</td>
<td>28 ± 11*</td>
<td>3.1 ± 0.5</td>
<td>52.9 ± 16.8</td>
<td>4.5 ± 0.6</td>
<td>−7.8 ± 3.6</td>
</tr>
<tr>
<td>2-APV</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>9 (human)</td>
<td>...</td>
<td>−14.9 ± 2.8</td>
<td>74 ± 21</td>
<td>23.9 ± 3.6</td>
<td>48.5 ± 8.6</td>
<td>4.2 ± 0.6</td>
<td>−10.5 ± 2.9</td>
</tr>
<tr>
<td>MK-801</td>
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</table>

LT decrease indicates light transmittance decrease during SD; SD$_{des}$ SD velocity. Slices treated with NMDAR antagonists were compared with contralateral control slices using paired t test (*$P<0.05$).
Figure 1. NMDAR blockade does not inhibit spreading ischemia (SI) (A) and spreading depression (SD)-like depolarizations under high extracellular potassium concentration ([K$_{ACSF}$]) (B). Changes of cerebral blood flow (CBF), [K$_{ACSF}$], and the direct current (DC) potential were recorded at a cranial window. Insets with higher temporal resolution (from hatched areas in the graphs) illustrate the delay of onset between the probes (arrows). Black traces, Caudal laser Doppler probe, and K$_{ACSF}$-sensitive/reference microelectrode. Gray traces, Rostral probes. SI was generated by hemoglobin and increased [K$_{ACSF}$] after systemic application of MK-801. SD-like depolarizations were generated by increased [K$_{ACSF}$] after administration of MK-801.
slices. The electrophysiological and optical parameters did not differ significantly. An example is given in Figure 3A.

The same protocol was followed in group 6 (n = 6), but MK-801 (20 μmol/L) was applied instead. The first SD-like depolarization occurred when [K+]o had reached 11.6 ± 3.1 mmol/L. No further SD-like depolarization was detected during perfusion with MK-801 at this [K+]ACSFl, contrarily to control slices. When [K+]ACSFl was further increased by 5 mmol/L, SD-like depolarizations occurred in all slices perfused with MK-801. Thus, although NMDAR antagonists shifted the dose–response curve for SD-like depolarizations evoked by high [K+]ACSFl, their efficacy to block SD-like depolarizations was significantly reduced by high [K+]ACSFl similar to the in vivo findings.

As previously reported,6 SD was completely blocked in slices perfused with physiological ACSF and either MK-801 (group 7, n = 6) or 2-APV (group 8, n = 6), in which SD was triggered by local microinjection of 3 mol/L KCl into layers II/III using a glass capillary. Repetitive SDs were inducible in all control slices.

**NMDAR Blockade Fails to Inhibit SD-Like Depolarizations in Human Slices Under High [K+]o**

After a stepwise [K+]ACSFl increase (2.5 mmol/L per 60 minutes), SD-like depolarizations occurred in human neocor-

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**Figure 2.** NMDAR blockade prevents the propagation of SD-like depolarizations from tissue with elevated extracellular potassium ([K+]o) into tissue with normal [K+]o. Changes of CBF, [K+]o, and DC potential were recorded at 2 cranial windows (black trace, caudal window; gray trace, rostral window). SD-like depolarizations were generated at the caudal window by superfusion with high [K+]ACSFl. These depolarizations traveled into the rostral window superfused with physiological ACSF. Left, SD-like depolarizations propagated from the caudal to the rostral window, indicated by the delay of onset at the probes. Right, After systemic application of MK-801, SD-like depolarizations were still generated by high [K+]ACSFl at the caudal window, whereas SD was inhibited at the rostral window.
When [K+] reached 23.9 ± 3.6 mmol/L (n=6), the threshold was statistically higher compared with rat neocortex (P<0.001, Student t test). Subsequently, MK-801 (20 μmol/L) was perfused at the elevated [K+]ACSF. No further SD-like depolarizations occurred during that period, whereas they were observed in neighboring slices that served as controls. Subsequently, [K+]ACSF was further raised by 5 mmol/L during continuous perfusion with MK-801, inducing SD-like depolarizations in all slices. An example is depicted in Figure 3B.
Discussion

We found that NMDAR antagonists did not block SD-like depolarizations or SI when [K+]o increased to concentrations similar to those in the ischemic penumbra in vivo or in hypoxic brain slices. Our findings may be relevant for neuroprotective strategies in brain trauma, stroke, and brain hemorrhage, in which the occurrence of SD-like depolarizations has been suggested, and for ischemic infants after SAH, which may be caused by SI.1–11 Pathological [K+]o elevations preceding SD-like depolarizations or SI in these conditions may be induced by energy depletion as in the ischemic penumbra, tissue disruption as in brain trauma, or [K+]o release from erythrocytolyis as after SAH.12 The higher threshold for SD-like depolarizations in human compared with rat brain slices may be related to anticonvulsant-induced or epilepsy-induced altered expression of signaling proteins. However, the latter seems unlikely, because the SD threshold is reduced in epilepsy models in human and rodent tissue.24

SD-like depolarizations may augment tissue damage.4,7 Because NMDAR antagonists block SD in normal tissue, they have been regarded as promising drugs to ameliorate the deleterious effect of SD-like depolarizations. NMDAR inhibitors reduced the frequency of SD-like depolarizations after experimental focal ischemia,4,16,17 but they had no effect on anoxic depolarization (AD).6,13,14 However, compared with their potent effect on “normal” SDs, the efficacy of NMDAR antagonists on SD-like depolarizations was lower.4,15–17 Likewise, we found that NMDAR antagonists increased the threshold for SD-like depolarizations, but their efficacy was dramatically reduced when [K+]o increased, implicating that under pathological conditions, SD-like depolarizations originating in tissue with elevated [K+]o, may not be blocked by NMDAR antagonists. Given the gradual evolution from AD to SD-like depolarizations to SD, these depolarizations may become more susceptible to NMDAR inhibitors as they propagate away from the compromised tissue, suggesting that SD-like depolarizations may still occur in the injured tissue under NMDAR blockade even though they may not be recorded in the infarct periphery. Notably, the therapeutic time window of NMDAR antagonists in some animal models of stroke closes well before the majority of SD-like depolarizations appears,25 suggesting that effects other than SD inhibition, eg, lowered posthypoxic oxygen consumption,26 may contribute to their neuroprotective effect. In contrast, it was recently demonstrated that after focal ischemia, delayed application of an NMDAR antagonist reduced infarct size and neuroprotection. J Neurosci. 2003;23:11602–11610.

In summary, we showed that in vivo, the efficacy of NMDAR inhibitors on SD-like depolarizations and SI was critically reduced by increased baseline [K+]o. In human and rat brain slices, NMDAR antagonists rendered the tissue less susceptible to SD-like depolarizations, but they did not inhibit SD-like depolarizations when baseline [K+]o was increased.

Acknowledgments

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References


Increased Extracellular K\(^+\) Concentration Reduces the Efficacy of N-methyl-d-aspartate Receptor Antagonists to Block Spreading Depression-Like Depolarizations and Spreading Ischemia

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