Small-conductance Ca2+ activated K+ channel activation reduces hippocampal damage after cardiac arrest

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ABSTRACT

Introduction: Small conductance Ca2+-activated K+ (SK) channel mutations negatively impact NMDA receptors in hippocampal CA1 neurons. We hypothesized that pharmacological activation of SK channel activity might protect ischemia-induced damage by decreasing NMDA receptor-mediated excitotoxicity. Using a well-characterized animal model, we examined the effects of SK channel activity (either genetically (SK2) or over-expressed) on SK channel activity and neuronal damage following cardiac arrest (CA). In addition, we examined SK channel knockout (SK2 KO).

Methods: Isoflurane-anesthetized (2%) adult male WT, SK2 OE, and SK2 KO mice were subjected to CA induced by intravenous (IV) KCl. During CA, brain temperature was maintained at 36.5 ± 0.5°C. After resuscitation, monitoring was initiated with IV epinephrine (0.15 mg/kg/min) and ventilation with 100% oxygen and chest compressions (rate 300/min). WT male mice were injected with SK2 OE (180 µg, Intraperitoneally). Mice were counted and examined for neuronal survival

Results: SK2 KO mice showed decreased neuronal damage by ~65% (50 ± 6.7 vs. 18 ± 3.3); WT versus SK2 OE). Similar results were observed in CA1 neurons. SK2 OE mice showed decreased neuronal damage by ~70% (18 ± 3.3 vs. 6.7 ± 1.0; P<0.05). SK2 OE treatment significantly reduced CA1 neuronal damage compared with vehicle treatment (33.9 ± 7.3 vs. 62.4 ± 7.3; P<0.05).

HYPOTHESIS

Cardiac arrest (CA) results in global cerebral ischemia that causes cognitive deficits. The hippocampal CA1 neurons are essential for cognitive functions and are vulnerable to cerebral ischemia.

Cell death following global ischemia is predominantly mediated by glutamate excitotoxicity through NMDA receptors.

We have demonstrated that small conductance calcium-activated potassium (SK) channels function as endogenous negative modulators of NMDA receptors in hippocampal CA1 neurons.

METHODS

Treatments to activate SK channel protect ischemia-induced damage by decreasing NMDA receptor mediated excitotoxicity.

RESULTS

Physiological and cardiac arrest related parameters

<table>
<thead>
<tr>
<th>EBIO</th>
<th>Vehicle</th>
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<tbody>
<tr>
<td>Average±SE</td>
<td>Average±SE</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>24.7±6</td>
</tr>
<tr>
<td>Total CA time (min)</td>
<td>9.7±1.4</td>
</tr>
<tr>
<td>Epinephrine (µg)</td>
<td>11.4±4.0</td>
</tr>
<tr>
<td>Epinephrine/BW (µg/µg)</td>
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</tbody>
</table>

Blood gas data at 30 min after CPR

<table>
<thead>
<tr>
<th>EBIO</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average±SEM</td>
<td>Average±SEM</td>
</tr>
<tr>
<td>pH</td>
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<tr>
<td>PaCO2</td>
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<tr>
<td>PaO2</td>
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<tr>
<td>HC03-</td>
<td>12.2 ± 0.8</td>
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<tr>
<td>BE</td>
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</tr>
<tr>
<td>Na</td>
<td>149.0 ± 1.4</td>
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<tr>
<td>K</td>
<td>5.7 ± 0.4</td>
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<tr>
<td>Cl</td>
<td>118.0 ± 1.2</td>
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<tr>
<td>Glu</td>
<td>324.3 ± 48.2</td>
</tr>
<tr>
<td>Lac</td>
<td>4.2 ± 0.9</td>
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Figure 1.
SK2 KO mice showed increased neuronal damage (50.6±7.3 vs. 36.9±6.5%); SK2-OE mice showed decreased neuronal damage (10.5±5.2% vs. 36.9±6.5% ; P<0.05)

CONCLUSIONS

These data indicate that genetic over-expression or 1-EBIO-mediated pharmacological activation of SK2 channels increase CA1 neuronal survival following CA. Therefore, SK2 channels may represent a new target for neuroprotection following cerebral ischemia.

REFERENCES