Role of Soluble Epoxide Hydrolase in Post-Ischemic Angiogenesis

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BACKGROUND

- Angiogenesis is a natural defense mechanism helping to restore oxygen and nutrient supply to damaged brain tissue.
- Cerebral ischemia induces cerebral angiogenesis, part of a vascular remodeling response that is necessary for regeneration and functional recovery. To take advantage of angiogenesis as a therapeutic target in stroke, it is important to understand the underlying molecular mechanisms.
- Epoxycisatrinic acids (EETs), P450 eicosanoids produced in brain by astrocytes, play an important role in blood flow regulation and protection after cerebral ischemia. EETs’ actions are terminated by soluble epoxide hydrolase (sEH).

In a previous study, we found EETs to be increased, brain perfusion improved and infarct size reduced after middle cerebral artery occlusion (MCAO) in sEH knockout (sEHKO) compared to WT mice.

METHODS

- Animals: male sEH knockout (sEHKO) and Wild type (WT) mice
- Mice underwent 45 min of right-sided middle cerebral artery occlusion (MCAO) via the intraluminal filament technique followed by 8 days of recovery.
- A battery of somatosensory and cognitive neurobehavioral tests were performed during recovery.
- Brains were processed (perfusion-fixation, 4% PFA, free-floating 6 µm cryosections) and stained for CD34, which identifies endothelial cells, as well as endothelial progenitor cells. Unbiased, stereology-based estimates of vascular density were obtained from the density of CD34-positive vascular profiles in these brain sections using computer-assisted optical dissector probe.

RESULTS

1. Higher density of new blood vessels in sEHKO mice brain

<table>
<thead>
<tr>
<th>Density of Vascular Profile</th>
<th>WT</th>
<th>sEHKO</th>
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<tbody>
<tr>
<td>Ischemic Core Cortex</td>
<td><img src="image.png" alt="Graph" /></td>
<td><img src="image.png" alt="Graph" /></td>
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<tr>
<td>Penumbra Cortex</td>
<td><img src="image.png" alt="Graph" /></td>
<td><img src="image.png" alt="Graph" /></td>
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<tr>
<td>Contralateral Cortex</td>
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Density of new blood vessels in penumbra and contralateral cortex, but not in ischemic core, was significantly increased in sEHKO compared to WT mice (* p<0.05, n=8 per group).

2. Improved recovery of motor activity after stroke in sEHKO mice

- sEHKO mice are significantly faster to move out of circle in day 1 and day 3 after 45 min MCAO compared to WT mice (* p<0.05, n=8, each).

3. No differences were found in Cylinder Test and Object Recognition Test between sEHKO and WT mice.

CONCLUSIONS

- sEHKO mice have higher post-ischemic angiogenic capacity.
- sEHKO mice perform better in the latency to move, but not the cylinder test or the object recognition test after stroke.

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HYPOTHESIS

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