ACE2 shedding in the central nervous system of hypertensive patients

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Angiotensin Converting Enzyme type 2

ACE2 gene: 40 Kb
- Located on X chromosome
- 18 exons
- metalloprotease activity: exon 9

ACE2 protein: 805 AA
- Only one catalytic domain
- 42% identical to ACE
- Strict carboxypeptidase
- transmembrane and secreted forms
- Receptor for the SARS virus

Hamming et al. J. Pathol. 2007
Towler et al. JBC 2004
Angiotensin Converting Enzyme 2 (ACE2) is expressed throughout the mouse brain.

Green: neuronal marker MAP2
Red: ACE2
Orange: co-localization
Brain ACE2 expression and/or activity are reduced in hypertensive animals

Yamazato M et al. Hypertension 2007;49:926-931
Xia H et al. Hypertension 2009;53:210-216
ADAM17 increases ACE2 shedding

DOCA-salt hypertension promotes ACE2 shedding in the brain of mice

* P<0.05 vs. NT

Is ADAM17 in the brain affected by DOCA-salt hypertension?

* P<0.05 vs. NT (non transgenic)

Brain Adam17 silencing reduces hypertension and restores baroreflex function

A

\[
\Delta \text{MAP (mmHg)}
\]

B

\[
\Delta \text{SBRS (msec/mmHg)}
\]

C

\[
\text{NT+Sham} \quad \text{NT+DOCA} \quad \text{NT+DOCA+siADAM17}
\]

\[
\text{ADAM17} \quad \text{γ-Tubulin}
\]

D

\[
\text{ACE2 activity (AFU/mg/min)}
\]

Working model
Questions:

1) Is ACE2 shedding taking place in the brain of hypertensive patients?

2) Can it be corrected by BP medications?
### Demographics

38 patients from LSU Interim Hospital Emergency Room  
11 patients from West Jefferson Hospital, Neurosurgery Department

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Black or African American</td>
<td>18</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>White</td>
<td>9</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Average age</td>
<td>37 ±2</td>
<td>40 ±3</td>
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<tr>
<td>Normotensive</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Hypertensive + BP medications</td>
<td>8</td>
<td>4</td>
<td>12</td>
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</tbody>
</table>
ACE2 activity is not detectable using ELISA in human cerebrospinal fluid

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Soluble ACE2 (ng/mL)</th>
<th>TNFα (pg/mL)</th>
</tr>
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<tbody>
<tr>
<td>C1</td>
<td>0.435</td>
<td>42.588</td>
</tr>
<tr>
<td>C3</td>
<td>1.875</td>
<td>22.918</td>
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<tr>
<td>C4</td>
<td>0.304</td>
<td>5.642</td>
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<tr>
<td>C5</td>
<td>2.48</td>
<td>51.383</td>
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<tr>
<td>C6</td>
<td>0.079</td>
<td>23.176</td>
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<tr>
<td>C7</td>
<td>-0.055</td>
<td>1.229</td>
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<tr>
<td>C9</td>
<td>-0.025</td>
<td>61.904</td>
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<tr>
<td>C10</td>
<td>0.427</td>
<td>298.48</td>
</tr>
<tr>
<td>C11</td>
<td>0.642</td>
<td>18.384</td>
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</tbody>
</table>
RAS Fingerprint™
(www.attoquant.com)
ACE2 in the main enzyme responsible for Ang-(1-7) formation in human CSF
ACE2 activity is increased in the CSF of hypertensive patients.
Summary & Conclusions

- Soluble ACE2 activity can be detected in the CSF of patients, using the RAS-Fingerprint™ technology, while current Elisa assays lack the sensitivity to do so.

- ACE2 shedding is taking place in the central nervous system of hypertensive patients and appears to be normalized in patients with controlled hypertension, therefore ACE2 activity in the CSF is correlated to hypertension.

- More specimens are necessary to study uncontrolled hypertension, as well as race, gender diversity and other factors.
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