Correlations of blood and brain biochemistry in phenylketonuria: Results from the Pah-enu2 PKU mouse

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BACKGROUND

Treatment monitoring in PKU is based on frequent blood phenylalanine (Phe) measurements, because (Brain) Phe is thought to be the predictor of neurocognitive and behavioural outcome in PKU.

However, blood Phe does not explain the variance in neurocognitive and behavioural outcome completely.

While the relationship between blood Phe and brain Phe has been well investigated, other correlations of blood markers and brain biochemistry in PKU are less well researched.

AIM

This study aimed to investigate the different relationships between blood and brain biochemistry in PKU mice.

METHODS

We collected data on blood and brain amino acid and neurotransmitter concentrations from 114 enu2 PKU mice.

We investigated the relationship between plasma Phe and brain biochemistry (brain Phe and neurotransmitters).

Moreover, we investigated the additional value non-Phe Large Neutral Amino Acids to explain brain biochemistry.

Analyses were done using (multiple) linear regression analyses.
**RESULTS**

Plasma Phe correlated strongly to brain Phe, significantly negatively to brain serotonin & norepinephrine and weakly to brain dopamine. Phe has the strongest correlation to brain biochemistry from all plasma markers in the multiple regression analyses. Adding other non-Phe LNAA to the equation did not considerably help explain brain biochemistry.

*Figure 1. Correlations of plasma Phe to brain biochemistry*

**Table 1: Correlations of blood markers, influxes and ratio’s to brain Phe concentrations.**

<table>
<thead>
<tr>
<th></th>
<th>B6</th>
<th>Adj. R²</th>
<th>BTER</th>
<th>Adj. R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasm Phe</td>
<td>0.936*</td>
<td>0.874</td>
<td>0.957**</td>
<td>0.912</td>
</tr>
<tr>
<td>Plasm Phe/LNAA ratio</td>
<td>0.892*</td>
<td>0.792</td>
<td>0.931*</td>
<td>0.865</td>
</tr>
<tr>
<td>Influx Phe</td>
<td>0.927*</td>
<td>0.857</td>
<td>0.910*</td>
<td>0.825</td>
</tr>
<tr>
<td>Plasm Tyr</td>
<td>0.126</td>
<td>-0.02</td>
<td>0.427*</td>
<td>0.167</td>
</tr>
<tr>
<td>Plasm Phe/Tyr ratio</td>
<td>0.675*</td>
<td>0.445</td>
<td>0.851*</td>
<td>0.719</td>
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<tr>
<td>Influx Tyr</td>
<td>0.760*</td>
<td>0.569</td>
<td>0.788*</td>
<td>0.614</td>
</tr>
<tr>
<td>Plasm Trp</td>
<td>0.430*</td>
<td>0.170</td>
<td>0.151</td>
<td>0.804</td>
</tr>
<tr>
<td>Plasm Phe/Trp ratio</td>
<td>0.700*</td>
<td>0.481</td>
<td>0.870*</td>
<td>0.752</td>
</tr>
<tr>
<td>Influx Trp</td>
<td>0.917*</td>
<td>0.838</td>
<td>0.817*</td>
<td>0.661</td>
</tr>
<tr>
<td>Plasm Phe/His ratio</td>
<td>0.887*</td>
<td>0.783</td>
<td>0.890*</td>
<td>0.788</td>
</tr>
<tr>
<td>Plasm Phe/Thr ratio</td>
<td>0.862*</td>
<td>0.739</td>
<td>0.920*</td>
<td>0.844</td>
</tr>
</tbody>
</table>
DISCUSSION & CONCLUSION

Plasma Phe is still best amino acid predictor of brain biochemistry in PKU mice.

Neurocognitive and behavioural outcome are not fully explained by blood or brain Phe, while correlations of blood and brain biochemistry in PKU are very strong.

Explanations could be that:
1) The Phe we measure in the clinic does not represent the constantly fluctuating Phe in the body.
2) Patients have different brain vulnerability to high brain Phe concentrations

Therefore, we need to look for additional parameters to explain brain biochemistry in PKU

Correspondence & link to full article

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