**Objective**

The aim of this study is to develop a PBPK brain model to explore the effects of various physiological functions, particularly the active transporters present within the blood-brain/cerebrospinal fluid barriers (BBB/BCSFB), on drug disposition in brain.

**Background**

Drug penetration from the circulating blood into the brain is primarily limited by the BBB/BCSFB, because of the existence of tight junctions as well as active efflux and uptake transporters at these barriers (Figure 1).

![Figure 1. Major drug transporters on BBB and BCSFB](image)

Drug disposition within the brain is further affected by CSF hydrodynamics, because the CSF is circulated within the cranial cavity, from the ventricles to subarachnoid spaces after secreted from the choroid plexus and then absorbed from the cranial and spinal sections (Figure 2).

![Figure 2. CSF hydrodynamics](image)

**Method**

Literature were reviewed to collate brain physiological and anatomical attributes as well as any information on transporter abundance and activities on the BBB and BCSFB. A 4-compartment diffusion-limited brain model was developed and implemented in Matlab Simulink®. The model divides CSF into 2 compartments namely cranial and spinal sections (Figure 3). The brain model was combined with a whole-body PBPK model, which has been established in the Simcyp Simulator.

Using the model, several scenarios were investigated to explore the effects of various physiological functions, particularly, the effects of transporters, on drug disposition in brain and CSF.

![Figure 3. Structure of 4-compartmental diffusion-limited brain model](image)

**Results**

The information on physiological and anatomical attributes were relatively rich, however there was a major shortcoming regarding the abundance of transporters and their activities (Tables 1 & 2).

![Table 1. Parameters availability in brain model](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intracranial blood</th>
<th>Brain mass</th>
<th>Cranial CSF</th>
<th>Spinal CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Flow rate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>pH</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Protein</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Enzyme</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

![Table 2. Abundance of active transporters](image)

<table>
<thead>
<tr>
<th>Transporters</th>
<th>P-gp</th>
<th>MRP4</th>
<th>BCRP</th>
<th>OATP1A2</th>
<th>OATP2B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBB</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>BCSFB</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Simulation outcome**

Various parameters were assumed in the simulation to explore the possible effects of physiological functions on the drug disposition in brain and CSF (Figures 4-6).

**- Effects of passive transport**

- Compound: Quinidine
  - Dose: iv, 200 mg
  - Fixed parameters:
    - $P_{S}=0.0021 L/hr$;
    - $C_{L}=14.419 L/hr$;
    - $Q_{in}=0.006 L/hr$;
  - Floating parameters:
    - $P_{S}=0.0000021 L/hr$;
    - $C_{L}=2.1 L/hr$;
    - $Q_{in}=0.014 L/hr$;

![Figure 4. Simulation of changed passive transport](image)

**- Effects of active transporters**

- Compound: Quinidine
  - Dose: iv, 200 mg
  - Fixed parameters:
    - $P_{S}=0.0021 L/hr$;
    - $P_{S}=0.0000021 L/hr$;
    - $P_{S}=0.300 L/hr$;
    - $C_{L}=14.419 L/hr$;
  - Floating parameters:
    - $P_{S}=0.0000021 L/hr$;
    - $C_{L}=0.042 L/hr$;
    - $Q_{in}=5.25 L/hr$;

![Figure 5. Simulation of changed active transport](image)

**- Effects of CSF hydrodynamics**

- Compound: Quinidine
  - Dose: iv, 200 mg
  - Fix parameters:
    - $P_{S}=0.0021 L/hr$;
    - $P_{S}=0.0000021 L/hr$;
    - $P_{S}=0.300 L/hr$;
    - $C_{L}=14.419 L/hr$;
  - Floating parameters:
    - $Q_{out}=0.014 L/hr$;
    - $Q_{out}=0.006 L/hr$;
    - $Q_{out}=14.4149 L/hr$;

![Figure 6. Simulation of changed CSF hydrodynamics](image)

**Conclusions and further development**

- Consistent with reported clinical studies, the model was able to show the disparities in drug concentration-time profiles in blood (or plasma), brain mass, cranial and spinal CSF which was related to drug properties, particularly transporter affinities.
- On the basis of observations, the 4-compartmental diffusion-limited brain model is now being incorporated within the Simcyp Population-based Simulator.

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