Blood brain barrier maturation: implications for drug development.

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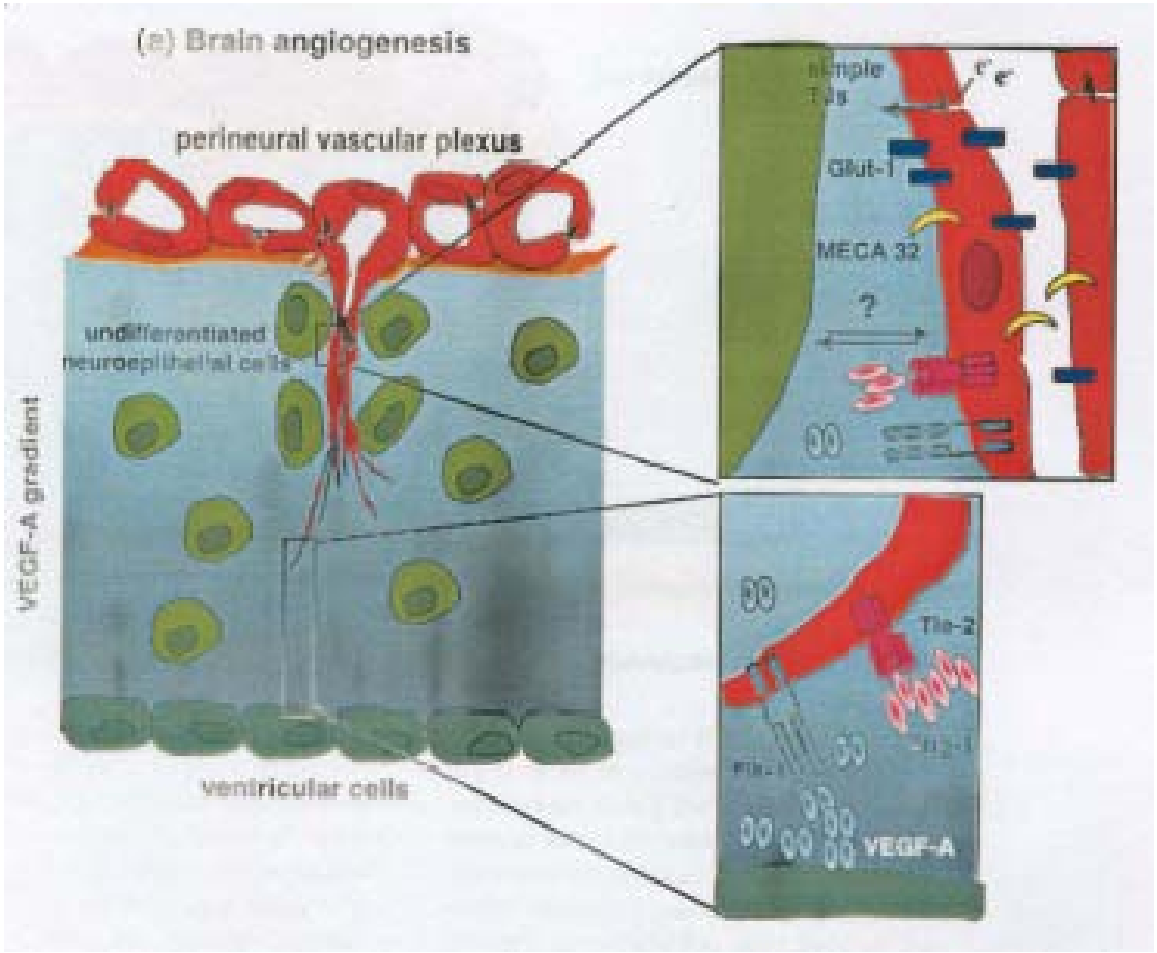
Modelling of BBB permeation / permeability

- Little data available in the literature on modelling BBB permeability in pediatric population.
  - Adult animal in-silico models available: total brain.
  - Potential area for investigation.
  - High level view of the area.
- In the absence of a modelling strategy how should starting dose be selected.

Stage 1



- Brain endothelial cells derived from the permeable vessels penetrate the nectoderm.
- Forms the intraneural vessel
- Angiogenic process.
- Lacks a BBB

(Engelhardt et al 2006., Blood brain interfaces: from Ontogeny to artificial barriers, Wiley-VCH Verlag GmbH).

Song et al 2002

Stage 2

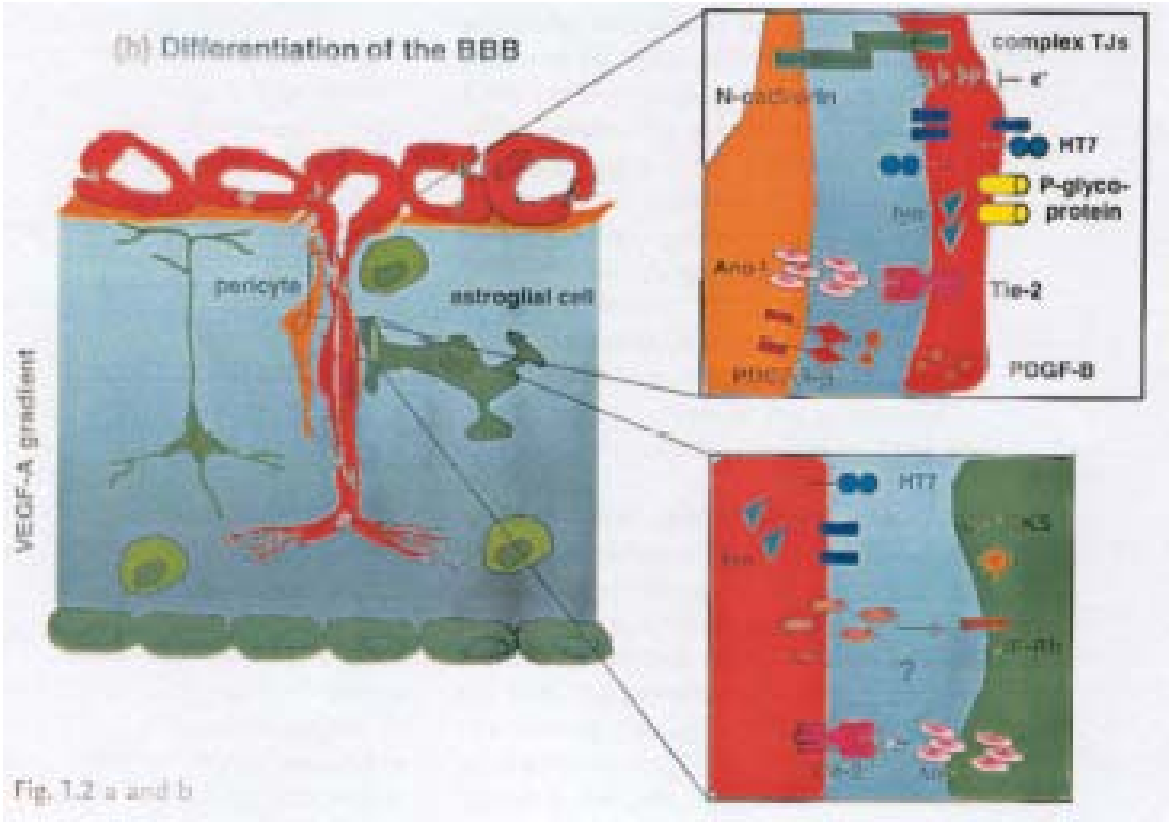
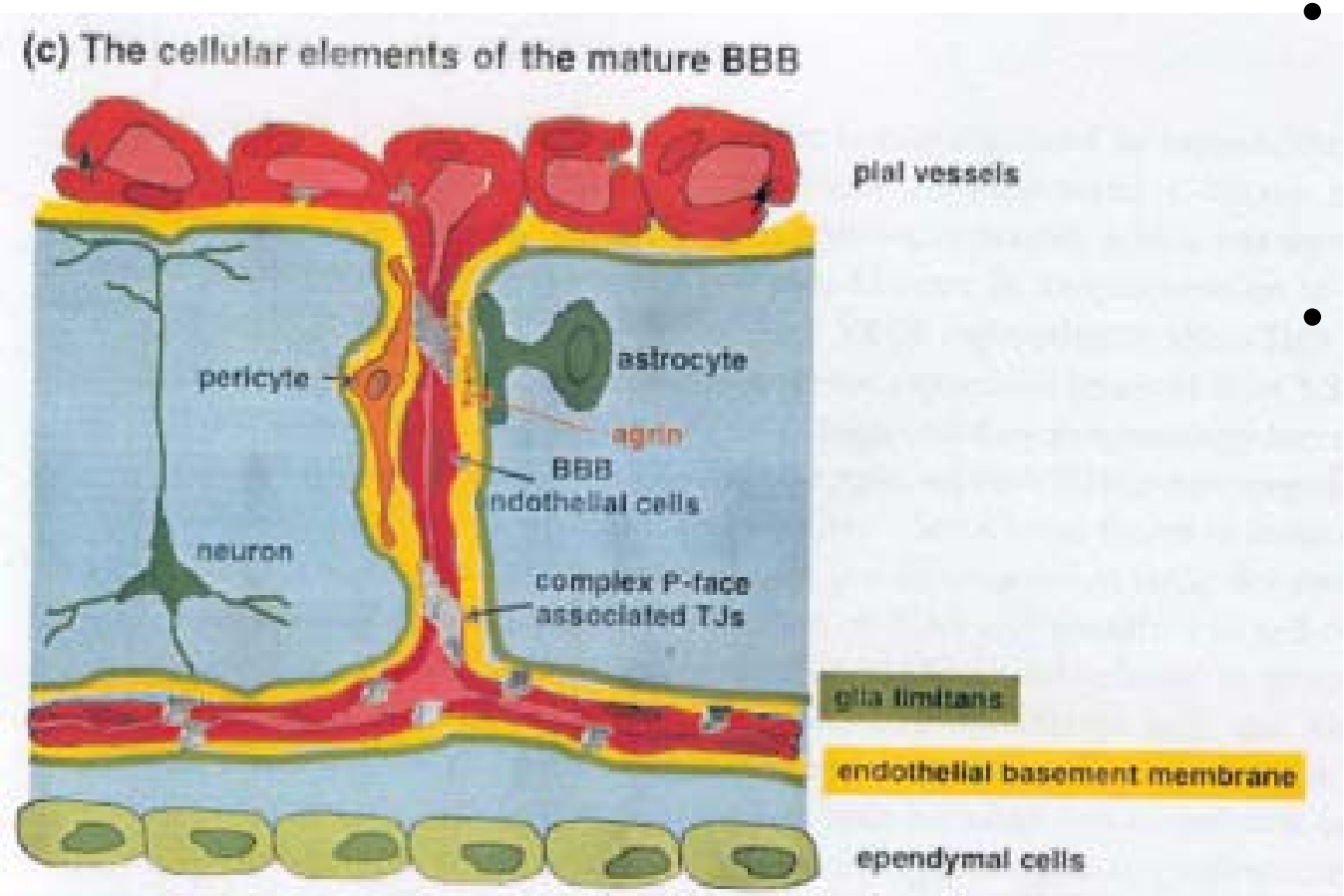


Fig. 1.2 a and b

- Evolution of the BBB phenotype.
- Establishment of complex tight junction between cells.
- Transport systems for hydrophobic compounds.

•(Engelhardt et al 2006).

Fully mature BBB



- Pericytes, which cover the endothelial cells.
- Basement membrane: protective role, electrostatic selective filter for charged macromolecules.
- Astro glial end feet, maintain BBB properties.

•(Engelhardt et al 2006).

BBB penetration data in young animals, relevance to pediatric population

Animals vs human.

BBB in the young animals vs human.

- Comparison of BBB maturation is difficult in different species (Engelhardt 2006).
  - Different rates of brain development in different species.
  - Birth is not a reliable marker of BBB development.
- Rat as an example:
  - Contrary to the human brain, glucose consumption in the rat brain is very low at birth (Nehlig et al 1997) .
    - Maximum growth velocity
  - At birth in humans peripheral nerves are fairly well myelinated, in rat there is little pre-natal myelination (Watson et al 2006) .
  - Differences in the temporal expression of P-gp (Schinkel et al 1994; Qin et al 1995)
  - Available data indicates rodent is not a good species to study BBB penetration data.

BBB penetration data in animals, relevance to the pediatric population.

- No consistent picture of the maturation of the BBB in animals.
  - Clear rat is not a good model.
- Given the controversy can a safety decision be based on animal data?
- Area for increased scientific understanding.

The blood brain barrier in the pediatric population.

- Increased BBB penetration frequently cited.
- Frequently based on pharmacodynamic observations in term, newborn infants, etc.
- Is BBB penetration really different?
- Alternative explanation
  - Overdose: mg/kg dose correction, formulation challenges, etc.
  - Overdose is not unusual in pediatric populations

Measures of BBB permeability in the pediatric population.

- Access to ECF concentrations in the brain is difficult:
  - PET imaging, etc can provide accurate determination of concentrations in the brain.
    - Total
    - Little / no data available.
    - Occupancy – gold standard
  - CSF data frequently used as surrogate of brain ECF concentrations.
    - CSF and ECF not identical.
    - Barriers different
    - Evidence of differences in concentrations for lumber and cisterna magna sampling.
    - However, is there a better measure?

A cross section of paediatric CSF data

- **Thiotepa** – age range 2.5 – 18 year (n=20) *Heideman et al 1989*.
  - Camparable to adult preclinical concentrations.
- **Vincristine** – age range 2.5-14.1 (n=17) *Kellie et al 2002*.
  - Poor penetration, equivalent to adult.
- **Carbamazapine** – age range? (n=?) *Huang et al 1997*.
  - Good CSF penetration
- **Thioguanine** – age range 1 – 9 years (n=41) *Lowe et al 2001*.
  - Paediatric CSF penetration in keeping with adult preclinical data.
- **Cilistatin** – age range 4month – 11 years (n=20) *Jacobs et al 1986*.
  - Similar in animals and adults, no co variance with age
- **Imipenem** – age range 4month – 11 years (n=20) *Jacobs et al 1986*
  - Similar in animals and adults, no co variance with age

- What little data that is available points to CSF penetration in adults and children >4months old as being similar.
- No exposure data available to support the hypothesis of increased BBB permeability <4months.

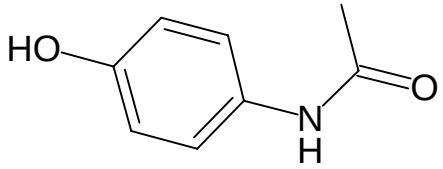
Concentration is CSF in pediatric population

- For small molecules / passive permeability
  - Generally the same as in adults.
    - Data only available for 4+ months.
    - Limited data.
  - No data available in the very young < 4month.

Modelling of BBB permeability vs age?

(van der Marel et al 2003. Eur. J. Clin. Pharmacol. 59 pp 279-302)

- Plasma to CSF equilibrium time
- Acetaminophen
- Median:
  - Age: median 12 months (75th percentiles - 3-62 months).
  - Size standardized to 70kg using allometric ¼ power model, general describes how 2 material are transported through the space filled network.



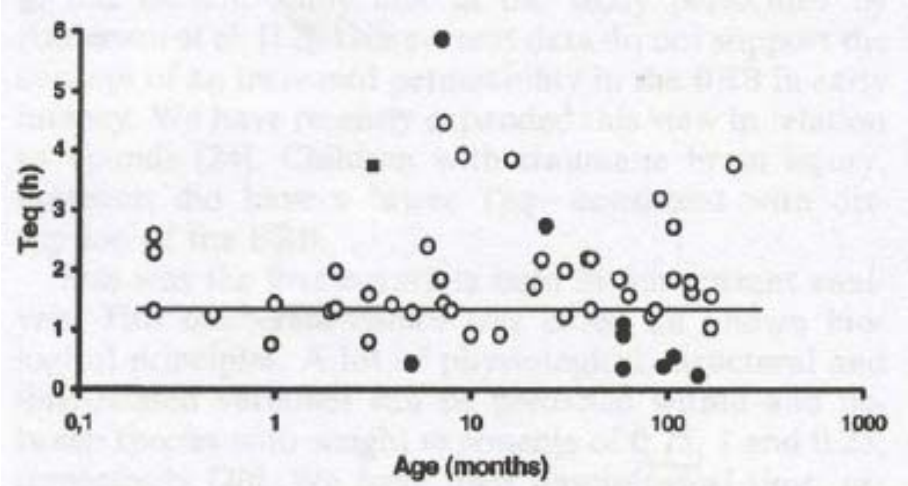


Fig. 2 Individual Bayesian Teq (plasma to CSF equilibration half-time) predictions (standardized to a 70-kg person) and their relationship to age for the complete pooled data set. Predictions from the current data set are shown as *x*. Predictions from data from Anderson et al. are shown as Δ. Standardized Teq does not change with age

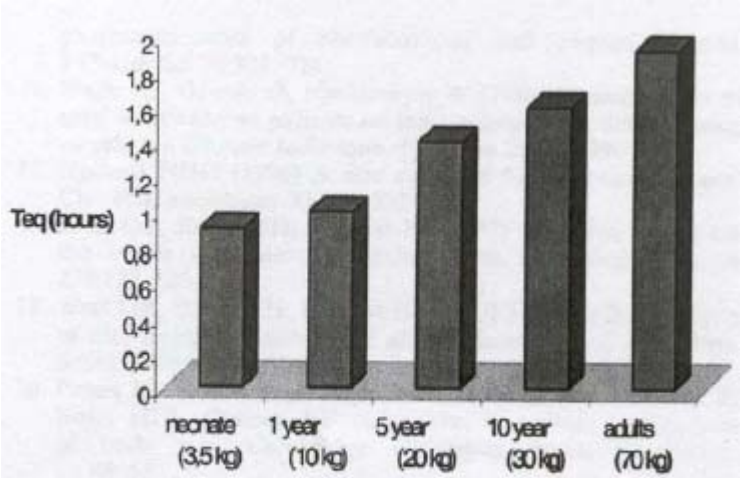


Fig. 5 Teq (h) expected for a neonate (3.5 kg), 1-year-old child (10 kg), 5-year-old child (20 kg), 10-year-old child (30 kg) and an adult (70 kg)

Does BBB permeability alter with age?

(van der Marel et al 2003)

- Conclusions:
  - Equilibrium half-life changes with age in children (lower).
  - Size rather than BBB maturation determines plasma to CSF equilibrium half-life.
  - Differences in equilibrium half-life can be readily scaled using allometric ¼ power rule.

Is the BBB more permeable in the pediatric population?

- Data indicates that BBB (B-CSF-B):
  - Quicker to equilibrate – scale using ¼ power rule.
  - No significant differences in BBB permeability.
  - The blood brain barrier in human matures at an early age (4months) .
- Insufficient data to understand risk in the very young (<4 months).
- Reported differences in pediatric side effect profile may be due to inaccurate / over dosing.

How do we safely administer compounds to the pediatric population?

- Theoretically, issue will be greatest with:
  - Low therapeutic index compounds
    - Establish therapeutic index in adult.
    - Consider potential for pediatric specific phenomena (ie. growth related toxicity).
    - Consider impact of eroding TI in pediatric population
  - Poor CSF / free plasma concentration ratios (<<0.5)
    - Immature animal data a poor platform for decision making on CNS penetration risk.
    - Understand CNS penetration in the adult population.
    - Consider potential for major increase in exposure if barrier is permeable.

Strategy

- For >4 months – consider as adults in terms of CNS penetration.
- For <4 months proceed with caution. Develop strategy to mitigate risk of unexpected CNS penetration – case by case.
  - Investigate BBB permeability in adults.
  - If large changes in BBB permeability are likely.
  - Consider if changes in equilibrium time will effect safety (¼ power rule).
- Make allowance for differences in pharmacokinetics
  - Allometrically scaled adult dose using body surface area, modelling, etc.
- Determine safe starting dose.
  - Corrected for maximum brain penetration so if adult 0.2, dose is 5 fold lower?