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Pilot Data on Brain-to-Blood Efflux of B-Amyloid Peptides in Man

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Background to the study

- Alzheimer’s disease (AD) is the most common cause of dementia and affects nearly 40,000 individuals in Ireland.
- The β-amyloid peptide (Aβ) plays a key role in the pathogenesis of the AD and the presence of Aβ plaques in the brain is diagnostic.
- The hypothesis posits that Aβ deposition is a critical factor in the disease process and that production and clearance of Aβ are key drivers of the disease.
- Flux of Aβ from the brain is believed to contribute to the overall level of Aβ within the brain and antibody mediated brain-to-blood efflux has been observed in animal models.
- Clearance of from the brain is believed to be mainly via the liver, kidney and spleen.
- Data from human studies indicate that about 6% of the Aβ pool present in the cerebrospinal fluid is cleared per hour.
- There are no data available on the magnitude of the cerebral output of Aβ peptides in man or the hepatic uptake.
- The aim of this work was to investigate if the concentration Aβ peptides differ in jugular venous plasma and arterial plasma and so estimate direct values for both brain-to-blood Aβ efflux and hepatic clearance in man.

Experimental Methods

- Blood samples were obtained as described.
- Plasma samples: These were available in connection with a previous study on brain sterol fluxes. Briefly, ten healthy males, mean age 29 years (range, 21–38 years) were recruited for this study and blood samples were taken after an overnight fast. Plasma was frozen at −80°C until required for analysis.
- Ethics: All experiments involving human volunteers were reviewed and approved by the ethics committees at the Huddinge Hospital and the Karolinska Hospital. Participants gave informed consent to participate in the study.
- ELISA for Aβ: Specific antibodies against Aβ1–40 and Aβ1–42 were used as primary antibodies. The reporter antibody was horseradish-peroxidase-linked anti-rabbit IgG and colour was developed with o-phenylenediamine. The detection limit for synthetic Aβ1–40 and Aβ1–42 was 1 pM. All samples were analyzed in the linear range of the ELISA.

Data Analysis: The concentration of Aβ1–40 and Aβ1–42 in the arterial and venous plasma was compared using a non-parametric approach. The significance level was set at 0.05. The molar concentrations of Aβ1–40 and Aβ1–42 were calculated. The percent extraction of individual Aβ species was calculated according to:

\[ \text{Percent extraction} = \left( \frac{C_v - C_a}{C_v} \right) \times 100 \]

Negative values were considered to represent a net output. Daily fluxes were estimated according to:

\[ \text{Daily extraction} = (C_v - C_a) \times \text{organ plasma flow} \]

For the purposes of this calculation the cerebral and hepatic plasma flow were set at 650 L/d and 1000 L/d respectively.

Discussion

- This is the first attempt to directly quantify the brain-to-blood passage of Aβ in man. The daily cerebral output of Aβ1–40 was estimated to be 1 ng d−1 and that of Aβ1–42 was estimated to be 3 ng d−1.
- Although the data was not statistically significant the values are in reasonable agreement with data from a transgenic rat model of 1.6 ng d−1 for Aβ1–40.
- There are two main limitations to this work:
  i) The main limitation in the current study is the small number of samples available which has affected the power of the study.
  ii) There is the limitation that the material analysed was collected in connection with a previous study on brain sterol homeostasis.
- Given the paucity of the data available we considered it prudent to commence these investigations on a pilot basis and use the data to design larger studies.
- Based on the data available in connection with this study we estimate that a sample size of 40 would be required to have an 80% power to detect a difference in percent extraction of 13.5%.
- While this is an ambitious number of participants for a relatively invasive procedure we believe that the data generated would be very valuable for the field.