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 brain² and antibody mediated brain-to-blood efflux has been observed in animal models¹.

Clearance of from the brain is believed to be mainly via the liver, kidney and spleen⁴.

Data from human studies indicate that about 6% of the Aβ pool present in the cerebrospinal fluid is cleared per hour⁵.

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 is different 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 described⁶.

Plasma samples: These were available in connection with a previous study on brain sterol fluxes⁷. Briefly, ten healthy males, mean age 29 years (range, 21–38 years) were recruited for this study and blood samples were taken over an overnight fast. Plasma was frozen at -80°C until required for analysis.

Ethics: All experiments involving human volunteers were 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.

Results

Figure 3. Sampling strategy for organ specific arterial and venous plasma. Blood samples were taken simultaneously from catheters inserted percutaneously and positioned as above.

Figure 4. Paired absolute values of Aβ₁₋₄₀/₄₂ in cerebral and hepatic plasma. In the cerebral circulation, greater concentration in the vein is consistent with output while the opposite applies in the hepatic circulation. Each number corresponds to an individual participant.

Figure 5. Absolute values of Aβ₁₋₄₀/₄₂ in cerebral and hepatic plasma and inter organ fluxes. In the cerebral circulation a negative percent extraction is equivalent to an output while in the hepatic circulation the opposite applies. No statistically significant difference were found using the Wilcoxon matched-pairs signed rank test.

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) A further limitation is 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.

References