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Cerebral Open Flow Microperfusion (cOFM) enables quantification of enhanced transport of brain-targeted nanocarriers across the intact blood-brain barrier

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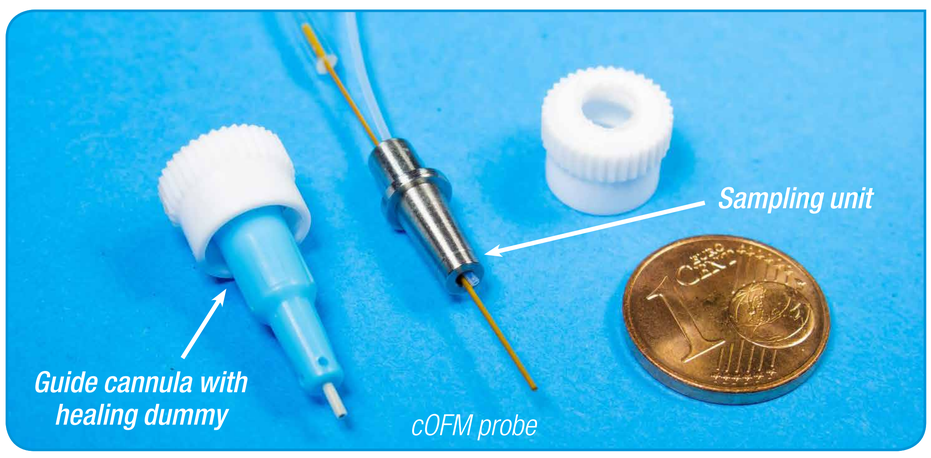
Background

The blood-brain barrier (BBB) protects the brain from harmful substances but also limits drug transport to the brain. One of the most promising methods to pass through the BBB is drug delivery by nanocarriers. The efficacy of nanocarriers is assessed by measuring drug concentrations directly in the brain, which is difficult with conventional techniques. Recently, cerebral open flow microperfusion (cOFM) was developed to monitor drug concentrations directly in the brain. cOFM can be used to sample drug irrespective of molecular weight, size or lipophilicity, without affecting BBB integrity.

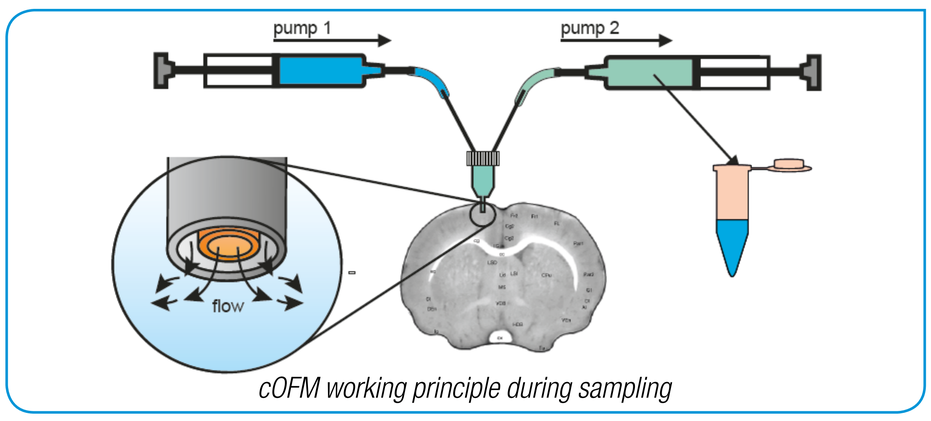
Aim

Compare transport of two doxorubicin formulations over the BBB when using brain-targeted nanocarriers (2B3-101) against non-targeted nanocarriers (Caelyx®).

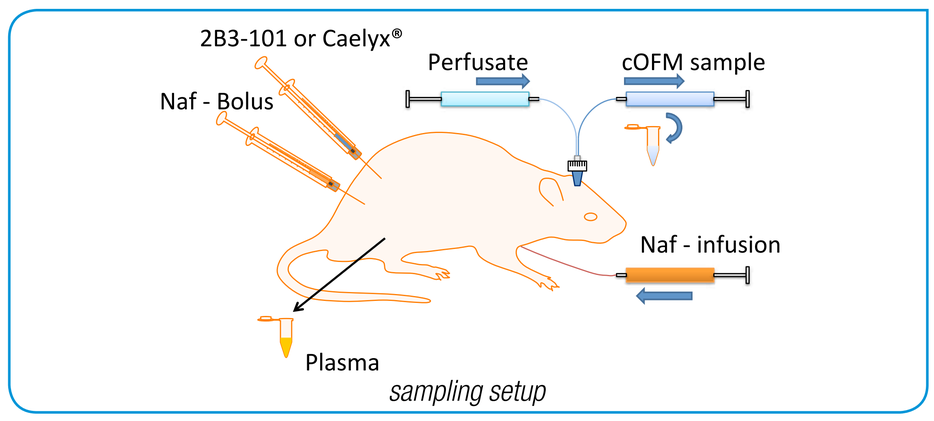


Methods

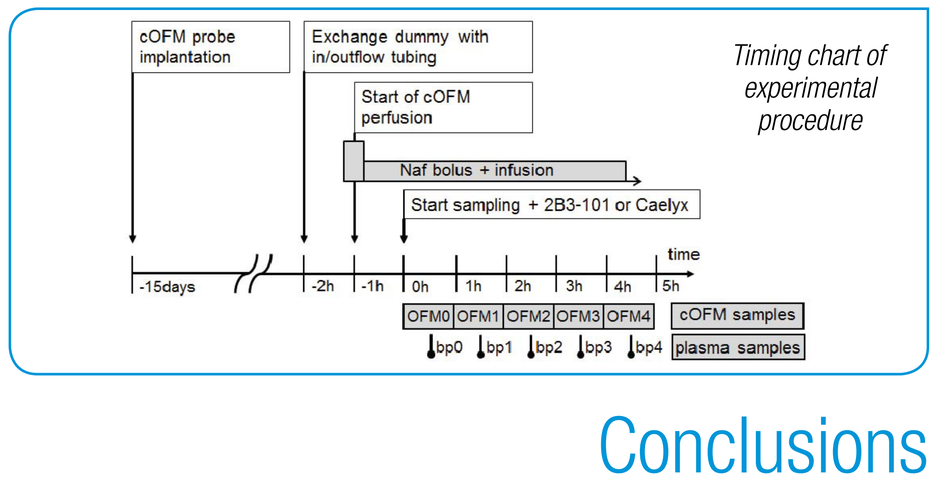
- 12 male Sprague Dawley rats were used in a blinded in-vivo study
- Two different doxorubicin formulations were compared:
  - 2B3-101 - glutathione pegylated liposomal doxorubicin (nanocarrier)
  - Caelyx® - similar formulation in a non-targeted form
- Naf was used as a marker for BBB intactness
- 15 days after cOFM probe implantation BBB integrity is re-established (Birngruber et al. 2013, Clinical and Experimental Pharmacology and Physiology)
- cOFM was used to sample brain interstitial fluid for 5h
- Doxorubicin and Naf levels were measured in cOFM samples
- Plasma samples were taken to assess systemic concentrations of doxorubicin and Naf in all animals



cOFM working principle during sampling



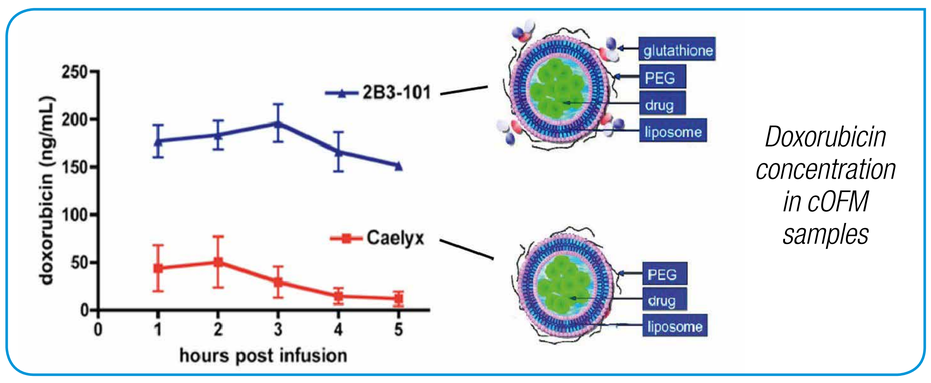
sampling setup



Timing chart of experimental procedure

Results

- The nanocarrier group showed a 4.8 higher concentration of doxorubicin in cOFM samples
- Stable Naf concentration indicated a intact BBB during the whole sampling
- Naf concentration in cOFM samples were similar in both groups



Doxorubicin concentration in cOFM samples

Conclusions

- Using cOFM, a new technique for cerebral sampling, we were able to demonstrate the significant enhancement of doxorubicin concentration directly in the brain when using a brain-targeted nanocarrier formulation.
- The use of Naf allowed the BBB intactness monitoring during the experiment.