



# PENETRATION OF QUINIDINE AT THE BLOOD-BRAIN INTERFACES

Franciska Erdő<sup>1,2</sup>, István Sziráki<sup>2</sup>, Mirabella Sike<sup>2</sup>, Péter Trampus<sup>2</sup>, Péter Imre<sup>1</sup>, Petra Molnár<sup>3</sup> and Péter Krajcsi<sup>2</sup>



<sup>1</sup>Faculty of Information Technology and Bionics, Pázmány Péter Catholic University – Budapest, <sup>2</sup>Solvo Biotechnology - Budaörs, <sup>3</sup>University of Szeged – Szeged, Hungary

**Introduction:** Quinidine (QND) is a widely used P-gp transporter probe substrate both *in vitro* and *in vivo* (1). Its brain exposure is enhanced by the co-administration of the P-gp inhibitor: PSC-833 in rats and mice (1, 2). Zhuang and coworkers described that the localization and function of Bcrp1, the other principal cerebral efflux transporter, are different in the blood-brain barrier (BBB) and in the blood-cerebrospinal fluid barrier (BCSFB) (3).

**Aim:** The aim of our study was to investigate whether the function of P-gp results in similar changes in the distribution of quinidine in brain extracellular fluid (ECF) and in the ventricular CSF in presence or absence of P-gp inhibitor.

**Method:** The blood, the brain ECF and the ventricular CSF concentrations of QND were monitored simultaneously by triple-probe microdialysis. QND was administered in a dose of 5 mg/kg i.v., and PSC-833 was given twice (2x2 mg/kg i.v.).

**Results:** The  $C_{max}$  values were detected at 60 min after the treatment both in the blood and in the CNS. The ECF and CSF concentrations of QND converged to the baseline after 3.5 hours in the control animals. Contrary, in the PSC-833 treated animals the QND concentrations decreased only moderately in the frontal cortex and did not reach the baseline in the lateral ventricle within the observation period. (3.5 hours). The calculated real tissue concentrations of QND in the CSF and the ECF were similar. However, after the combination treatment (QND+PSC-833), the ECF levels markedly increased, while the CSF levels although also increased but in much smaller degree. Also the characteristics of the curves were different.

**Discussion and conclusion:** Our results indicate that effect of chemical blocking of P-gp at the BBB and BCSFB resulted in increased drug levels both in the ECF and the CSF. However, the elimination of QND from the brain tissue was much slower than that was from the CSF. The observations that despite the different orientation of P-gp in the BBB and the BCSFB there is some correlation between the changes in the ECF and CSF concentrations of QND suggest that at least for compounds of decent passive permeability there is a substantial transport between these compartments.

## References:

- 1) Sziráki I et al, J Biomol Screen. 2011, 16(8):886-94.
- 2) Sziráki I et al, J Biomol Screen. 2013 18(4):430-40.
- 3) Zhuang Y et al, Cancer Res. 2006 Dec 1;66(23):11305-13

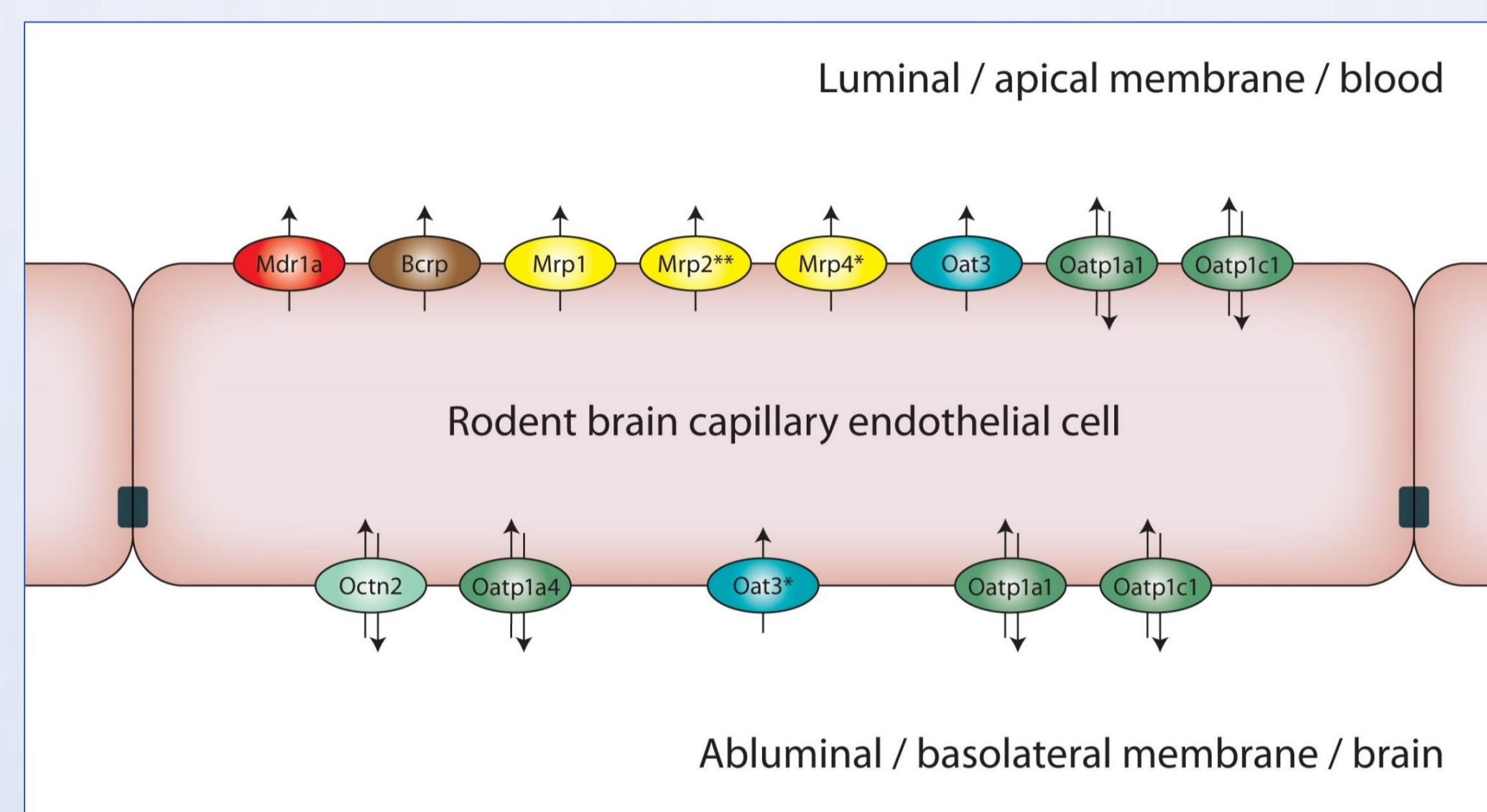


Fig.1 Schematic representation of membrane transporters in endothelial cells at the rodent blood-brain barrier

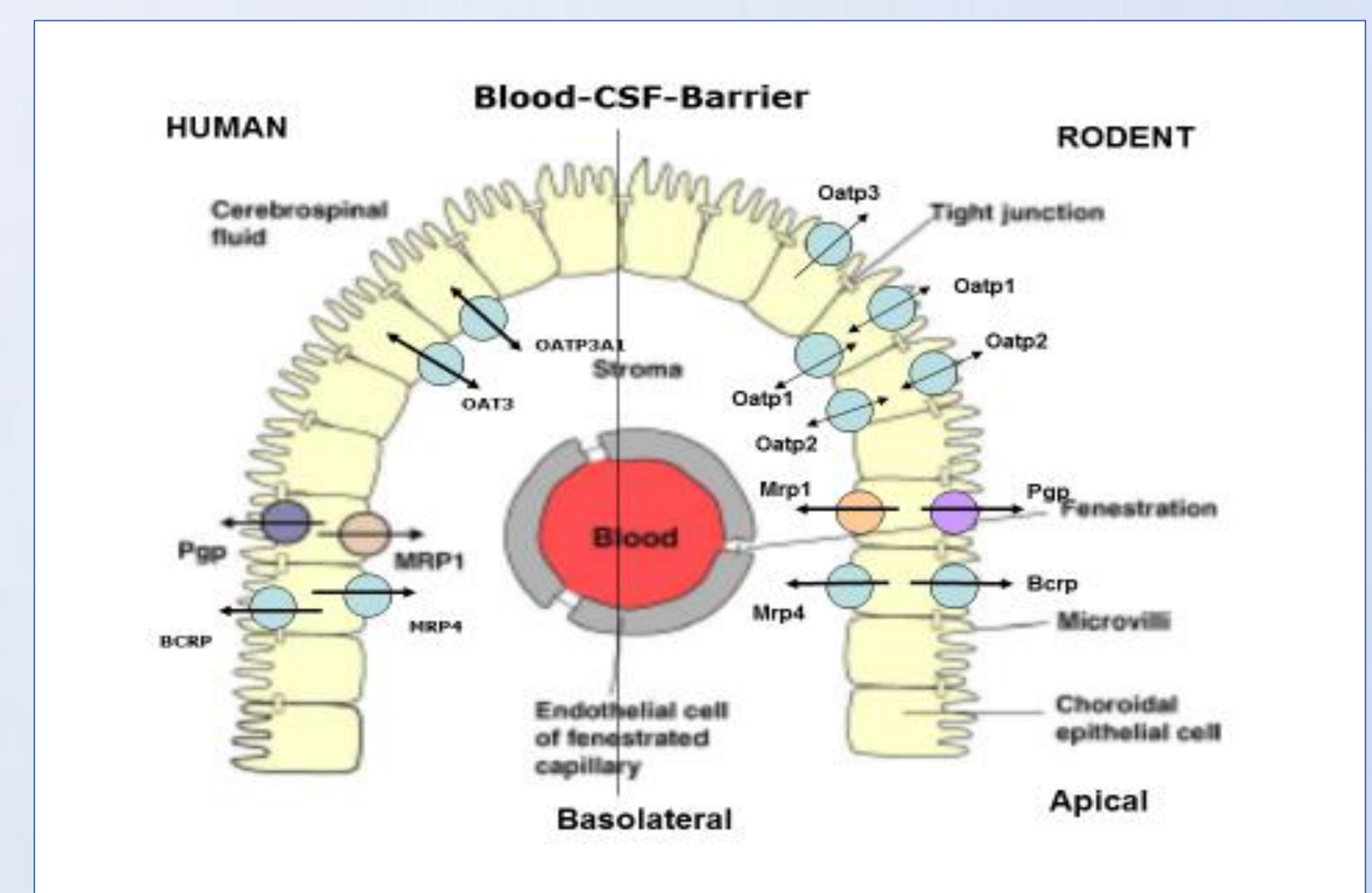


Fig.2 Schematic representation of membrane transporters in human (left) and rodent (right) choroid epithelial cells at the blood-cerebrospinal fluid barrier

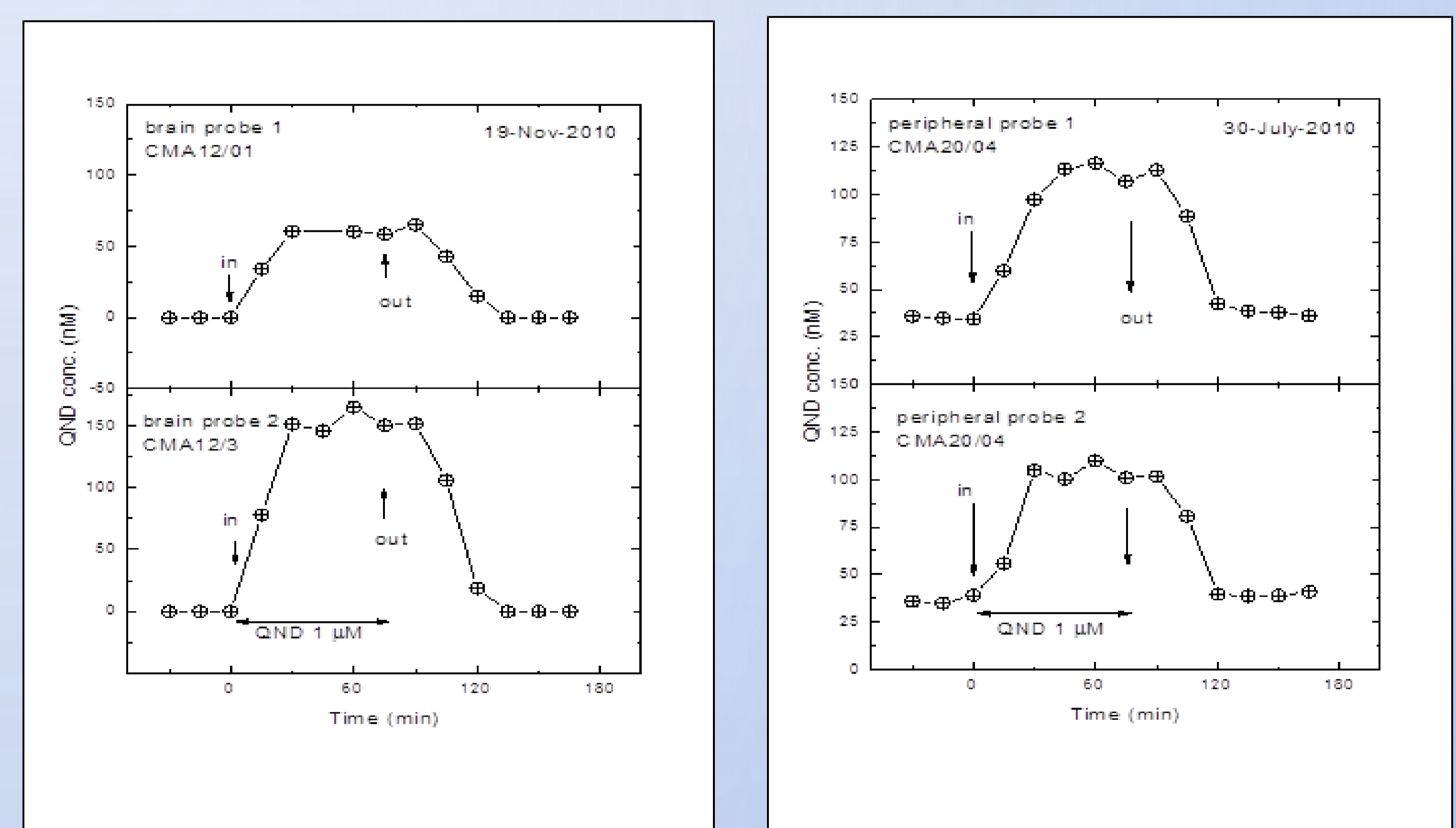


Fig.3 In vitro calibration of the microdialysis setup for Quinidine measurement for a triple probe microdialysis study. In vitro recovery of ventricular (CMA12/01), cortical ((CMA12/03) (left panel), and peripheral (CMA20/04) (right panel) probes.

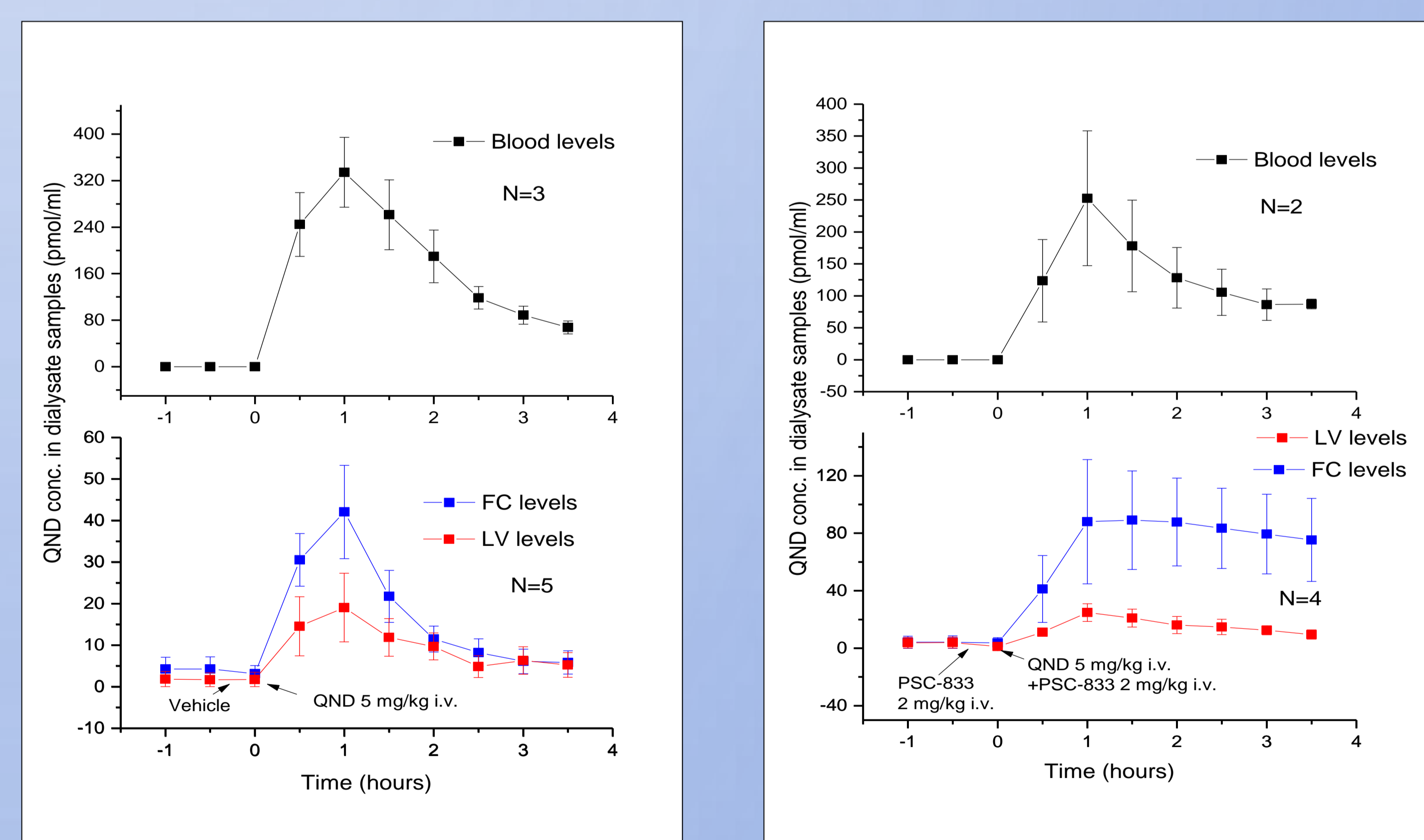


Fig.4 Concentration-time profiles of quinidine after IV administration in rats. The concentration changes are monitored in the blood, brain frontal cortex (FC) and lateral ventricle (LV) in control group (left panel) and in inhibitor treated (right panel) animals.

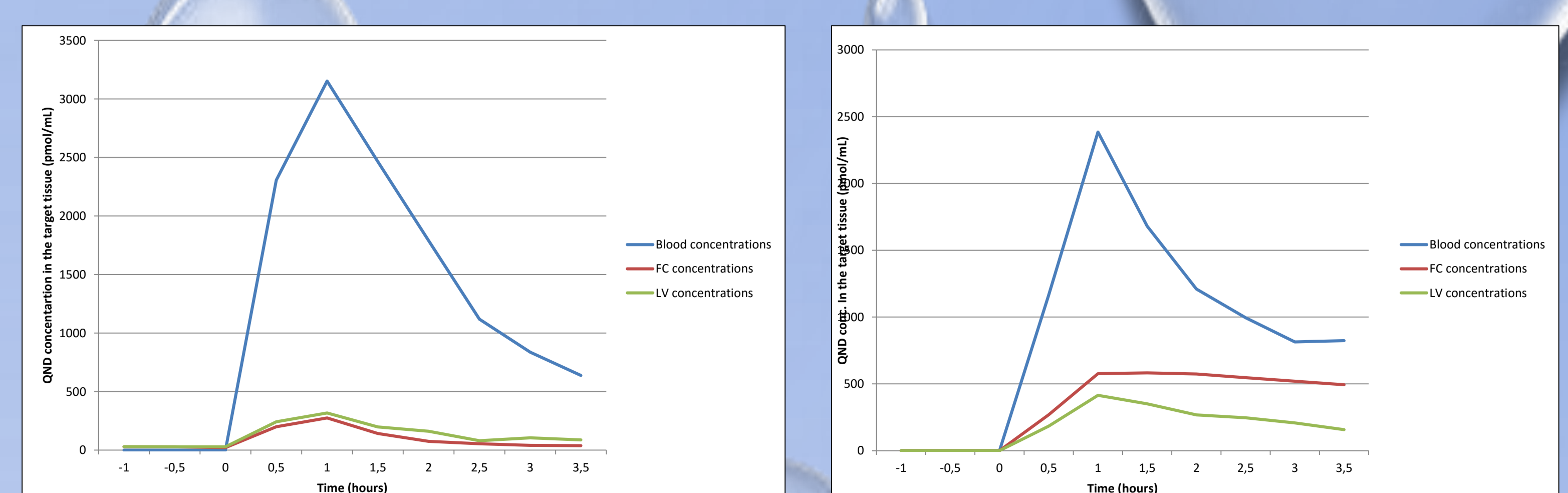


Fig.5 Concentration-time profiles corrected by relative recoveries for the three different microdialysis probes (CMA12/01; CMA12/03; CMA20/04) for quinidine after IV administration. These data represent the real tissue concentrations at the site of probe placement.