

P-GLYCOPROTEIN FUNCTION IN THE BLOOD-BRAIN BARRIER OF EPILEPTIC RATS

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Introduction

In chronic epilepsy, about 20%–40% of all patients develop resistance to anticonvulsant drug treatment during the course of their disease. Pharmacoresistance occurs in nearly all types of epileptic syndromes and is not limited to a specific drug or drug class, but rather to a wide variety of different antiepileptic drugs. The transporter hypothesis contends that the expression or function of multidrug efflux transporters at the blood-brain barrier (BBB), such as P-glycoprotein (P-gp) in the brain is augmented, leading to impaired access of antiepileptic drugs to CNS targets.

Study design and data analysis

Male Sprague-Dawley rats were treated with kainic acid to induce epilepsy (n=22) or with saline (n=20). At 1 week after treatment, each rat underwent a PET study with (R)-[¹¹C]verapamil. The P-gp inhibitor tariquidar, 15 mg/kg, was administered 20-30 minutes prior to the start of the (R)-[¹¹C]verapamil scan in half of the rats of each group. Blood samples were withdrawn during the PET scan and analyzed with regard to radioactivity in whole blood and plasma, and for labelled metabolites in plasma.

Logan analysis and compartmental modelling using a one (1T2K) and two (2T4K) tissue compartment model was applied. The input curve was corrected for all metabolites, for polar metabolites or not at all. Akaike information criterion, visual inspection, parameter estimates and precision was used to compare different modelling approaches. The estimates were compared between naïve and epileptic rats as well as between tariquidar treated and untreated rats.

Results

Differences in metabolism and plasma clearance of (R)-[¹¹C]verapamil between naïve and epileptic tariquidar untreated and treated rats were small. Pretreatment with tariquidar increased the brain (R)-[¹¹C]verapamil uptake and resulted in a 10-fold increase in the brain-to-blood partition coefficient (volume of distribution, V_T , Table 1) in both naïve and epileptic rats. In the tariquidar treated rats there was a small tendency towards slower uptake (K_1) and wash-out (k_2) of verapamil from epileptic rat brains than from naïve rat brains.

Aim

To compare the brain distribution of (R)-[¹¹C]verapamil, a tracer of P-gp function, in naïve and epileptic rats in order to assess possible differences in P-gp function at the BBB between these two groups.

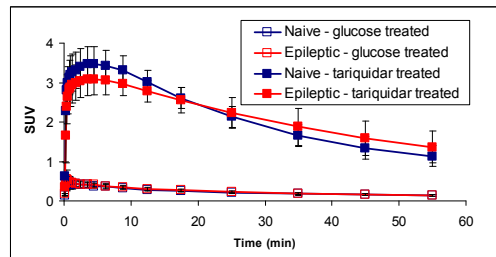


Figure 1. SUV profiles in the brain in the four groups. There was no difference between the naïve and epileptic control rats (glucose treated). The tariquidar treated epileptic rats had somewhat slower uptake and elimination of (R)-[¹¹C]verapamil than the naïve tariquidar group.

Table 1. Parameter estimates (SD) using complete metabolism correction of the input curve. The V_T estimates were similar across models. Inter-animal variation in parameter estimates was large for the 2T4K model.

Parameter estimates	Naïve glucose treated	Epileptic glucose treated	Naïve tariquidar treated	Epileptic tariquidar treated
<i>Model - Logan</i>				
V_T	0.94 (0.17)	0.94 (0.16)	10.5 (1.1)	10.7 (1.4)
<i>Model - 1T2K</i>				
K_1	0.08 (0.04)	0.09 (0.03)	0.94 (0.19)	0.68 (0.19)
k_2	0.12 (0.05)	0.12 (0.06)	0.09 (0.02)	0.06 (0.02)
V_T	0.70 (0.13)	0.70 (0.14)	10.4 (1.0)	10.5 (1.4)
<i>Model -2T4K</i>				
K_1	0.16 (0.15)	0.21 (0.15)	1.50 (0.49)	0.96 (0.36)
k_2	1.45 (2.17)	2.29 (2.17)	1.70 (0.49)	0.92 (0.96)
k_3	0.42 (0.46)	0.63 (0.42)	1.41 (1.07)	0.95 (0.69)
k_4	0.07 (0.46)	0.37 (0.95)	0.17 (0.04)	0.27 (0.46)
V_T	1.04 (0.38)	0.92 (0.16)	11.0 (1.1)	11.2 (1.4)

The Akaike information criterion, Table 2, indicated that the best model fit was obtained using a 2T4K-model with complete metabolite correction. Using this model, however, inter-animal variability in the parameter estimates was large. All three modelling approaches (1T2K, 2T4K and Logan) resulted in similar V_T estimates (Table 1).

Table 2. Akaike information criterion (lowest value = best model). The 2T4K model performed better than the 1T2K model for all treatment groups. All types of input corrections performed well for the two control groups (glucose treated). For the tariquidar treated groups the complete metabolite correction was found to be superior

Input curve correction	Naïve glucose treated		Epileptic glucose treated		Naïve tariquidar treated		Epileptic tariquidar treated	
	1T2K	2T4K	1T2K	2T4K	1T2K	2T4K	1T2K	2T4K
Complete metabolism correction	391	381	397	385	435	405	432	408
Polar metabolite correction	388	380	395	384	434	421	430	415
No metabolite correction	388	380	395	384	435	425	430	417

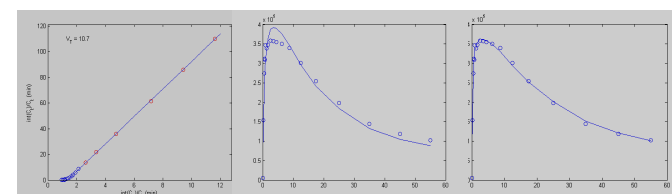


Figure 2. Model fits; Logan (left), 1T2K (middle) and 2T4K (right) for a naïve tariquidar treated animal.

Discussion and Perspectives

No major difference in P-gp function was observed between naïve and epileptic rats. However, PET scans were performed 1 week after induction of epilepsy. Therefore, it cannot be ruled out that P-gp function may be altered at other time points after induction of epilepsy.

The best model fit was obtained with a 2T4K model. However, there was a large inter-animal variation in parameter estimates for all groups. A population modelling approach (e.g. using NONMEM) in which inter-animal variability is determined in parallel with the structural model, should be investigated to assess the possibility of obtaining precise parameter estimates using a two compartment model.

Conclusion

P-gp function in naïve and epileptic rats appeared to be similar. Therefore, this study did not confirm the hypothesis that P-gp plays a major role in limiting brain uptake of P-gp substrates, e.g. anti-epileptic drugs, in epilepsy.

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