In vivo characterization of brain phenotypes associated with two-pore domain K+ channel (K2P) gene disruption

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Introduction

Potassium channels are involved in a wide range of cellular functions in both excitable and non-excitable cells. Among them, K_2P channels, recently described as background channels, have the particular role to maintain the resting membrane potential. Two members of this family, TREK-1 and TRAAK, mechano-gated and lipid-sensitive, seem to be involved in neuroprotective pathways. The aim of our study was to investigate the specific physiological functions of TREK-1 and TRAAK in brain, by studying the consequences of their deletion on the cerebral phenotype of knock-out mice.

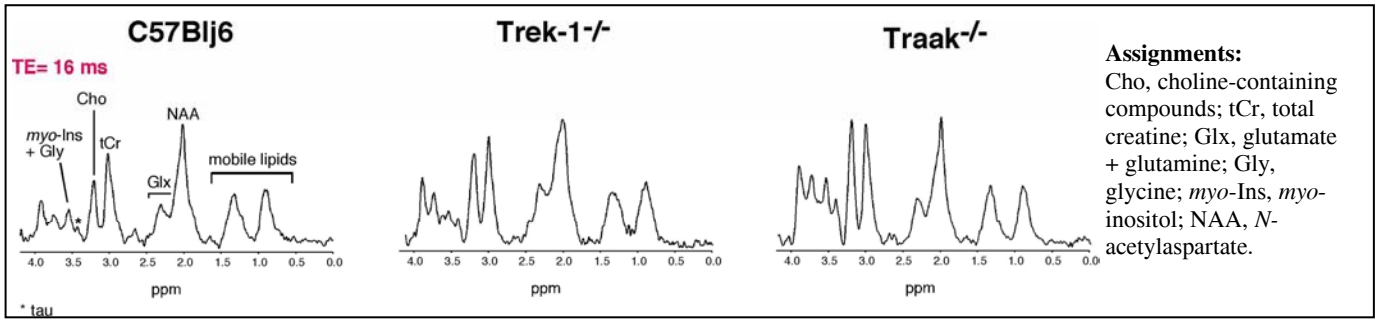
Material and Methods

C57Blj6, Trek-1$^{-/-}$ and Traak$^{-/-}$ mice were explored on a 4.7 T horizontal Bruker 47/30 AVANCE Biospec MR system (Bruker, Ettlingen, Germany). The MRI protocol included, multi-slice T_2-weighted images, diffusion and pulsed arterial spin labeling perfusion MRI of brain. *In vivo* metabolic explorations included ^{1}H-MRS (PRESS sequence with TE=16 ms and TE=135 ms) and ^{31}P MRS.

Results

We compared brain morphologic and metabolic profiles of Trek-1$^{-/-}$ and Traak$^{-/-}$ mice to those of the background strain (C57Blj6 mice) used to engineer the mutated animals. No significant difference was observed in brain structures among the three strains. A volumetric analysis of cerebral structures showed no statistical difference, despite a trend for a larger hippocampal volume for Traak$^{-/-}$ mice. ADC maps revealed that Trek-1$^{-/-}$ mice have significantly higher value of ADC in cortex. Perfusion maps displayed higher values of CBF in Trek-1$^{-/-}$ mice, though not reaching statistical significance.
From a metabolic point of view, ^{1}H-MRS unveiled major differences among the three strains. Indeed, Traak$^{-/-}$ mice showed significantly higher levels of choline, taurine, creatine and *myo*-inositol than Trek-1$^{-/-}$ and C57Blj6 mice (Figure 1).

Figure 1: Typical brain ^{1}H MRS of the different mouse strains



Discussion

This study, correlating for the first time brain morphology and metabolism, to Trek-1 and Traak deletion, establishes a direct link between K_2P and cerebral neurochemistry. Our metabolic findings indicate that TRAAK deletion significantly modifies brain metabolism and suggest an involvement of TRAAK in the regulation of several major cerebral metabolites. On the contrary, TREK-1 deletion does not seem to generate any significant metabolic modification, at least in the absence of any pathological or stressful context.