Comparative response to focal cerebral ischemia of C57Blj6, Trek-1-/- and Traak-/- mice

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Introduction

K_2P channels are widely distributed in CNS. They are involved in many physiological processes and show various regulatory mechanisms. Two members of this family, TREK-1 and TRAAK, are activated by potent neuroprotectors such as polyunsaturated fatty acids. The disruption of their genes leads to a modified sensitivity to ischemia, which suggests a role for them in the pathophysiology of cerebral ischemia. Our aim was to determine the effects of this gene disruption in a murine model of cerebral stroke.

Subjects and Methods

Six-month old male C57Blj6, Trek-$1^{-/-}$ and $Traak^{-/-}$ mice were used. Focal cerebral ischemia was induced by reversible middle cerebral artery occlusion. Mice were explored on a 4.7 T horizontal Bruker 47/30 AVANCE Biospec MR system. MRI included multi-slice T_2-WI, T_2*-WI, diffusion MRI, perfusion MRI, and angiography (performed at 11.75 T). Metabolic explorations included ^{1}H-MRS and ^{31}P-MRS.

Results

MR angiography validated the surgical procedure (Figure 1).

Figure 1 : MRA before, during and after mcao in a C57blj6 mouse

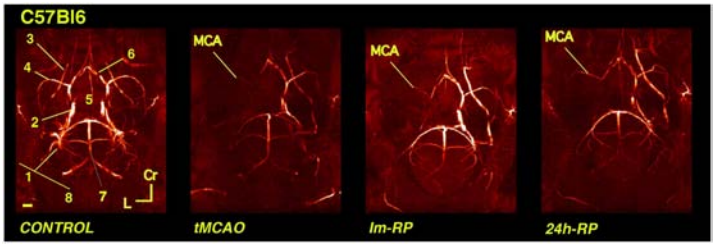


Figure 2 : Examples of T_2-weighted images of a C57Blj6 mouse

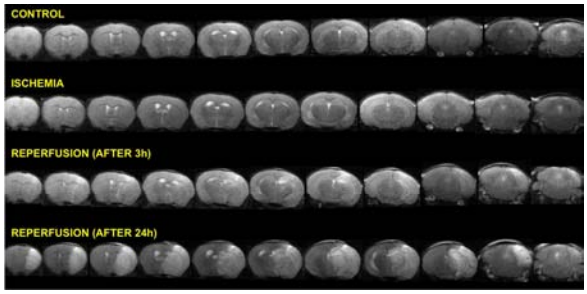
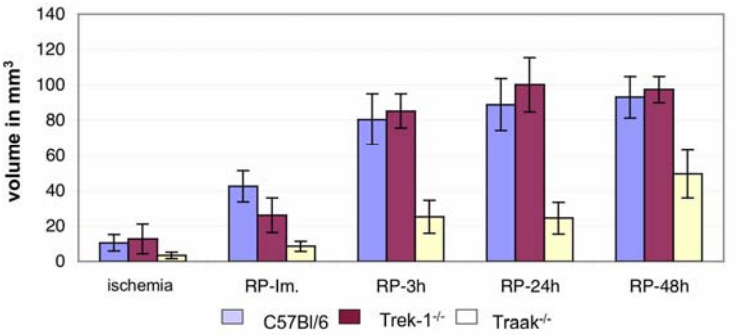


Figure 3: Comparison of infarct volumes



T_2-weighted images were used to quantify cerebral infarct (Figure 2). A smaller infarct was observed in $Traak^{-/-}$ mice (Figure 3), whereas Trek-$1^{-/-}$ mice showed higher volumes of infarct when compared to the control strain.

From a metabolic point of view, C57Blj6, Trek-$1^{-/-}$ and $Traak^{-/-}$ mice showed high lactate upon ischemia that could persist up to 48 h after reperfusion in Trek-$1^{-/-}$ mice, whereas $Traak^{-/-}$ mice recovered after 3 h. In addition, reduced levels of N-acetylaspartate and choline were observed in C57Blj6 and Trek-$1^{-/-}$ mice. Marked impairment of energy metabolism was observed in C57Blj6 and Trek-$1^{-/-}$ mice but was less important in $Traak^{-/-}$ mice. After reperfusion, a rapid recovery of the phosphocreatine level was observed in $Traak^{-/-}$ mice, whereas the amelioration was delayed in C57Blj6 and was not observed in Trek-$1^{-/-}$ mice after 48 h.

Discussion:

Disruption of TREK-1 gene leads to a higher vulnerability to ischemic insults whereas that of TRAAK seems associated with resistance to brain damage. Our findings suggest that specific pharmacological modulation of these K^+ channels may represent a promising therapeutic target for treatment and/or prevention of ischemic damage.