CELLULAR PRION PROTEIN PROTECTS AGAINST SEIZURE IN VIVO

Landemberger, M.C.[1], Machado, C.F.[1], Lobão-Soares, B.[2], Mallucci G.[3], Chesebro, B.[4], Walz, R.[5], Martins, V.R.[1]
[1]LICR, SP, Brazil; [2]USP RP, Brazil, [3]INN London, UK; [4]NIA/ID, Hamilton, USA
[5]UFSC, SC, Brazil.

The ablation of the Prion Cellular(PrP^C) gene enhances neuronal excitability of the hippocampus *in vitro*. We evaluated the contribution of PrP^C levels for seizure sensitivity by intraperitoneal administration of kainic acid(KA) or pentylenetetrazol(PTZ) in two constitutive PrP^C knockout mice(*ZPrnp*$^{0/0}$ and E*Prnp*$^{-/-}$),two post-natal PrP^C knockouts(CreTg37 and CreTg46) and their respective wild-type controls(WT) andTg20 animals that express six times more PrP^C than WT. All *ZPrnp*$^{0/0}$ mice developed seizures after 7.5mgKA/Kg treatment while 12.5mgKA/Kg is necessary to induce this phenotype in 85% of WT animals and 25mgKA/Kg induces seizures in 40% of the Tg20 mice(n=15,p<0.001). At 10mg/kg, KA stimulated seizures in 73% of E*Prnp*$^{-/-}$ mice(n=15) against 7% of controls(n=15,p<0.001) and in 20% of heterozygous(n=20,p=0.287). In CreTg37, 10mgKA/kg induces seizures in 100%(n=10) against 27% of controls(n=11,p=0.001) and in 80% of CreTg46(n=10) compared with 58% of controls(n=12,p>0.05). The mortality after seizures caused by treatment with 40mgPTZ/Kg was 85% in *ZPrnp*$^{0/0}$ mice against 20% of WT(p=0.005) and 0% in Tg20 mice(n=10,p<0.001). The mortality was 50% in E*Prnp*$^{-/-}$ mice and 6% in their respective WT(p=0.035). In CreTg37, the mortality after seizures was 75%(n=12) against 10% of controls(n=10,p=0.004) while 27% in of CreTg46(n=11) died against 20% of their controls(n=10,p=1.0). These data demonstrate that PrP^C expression is directly correlated to seizure sensitivity using different lines of PrP^C ablated animals or transgenic mice overexpressing PrP^C.
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