Altered hippocampal expression of calbindin-D-28k and calretinin in GABA(B(1))-deficient mice

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Balb/c GABA(B(1))(-/-) mice develop complex epileptiform activity, including spontaneous and audiogenic generalized seizures, 6-8 weeks after birth. The neuronal systems involved in these epilepsies have not been identified yet. Because the hippocampus is critically involved in epileptiform activity, we now investigated whether this brain region exhibits seizure-related alterations. Using semi-quantitative immunohistochemistry, we studied the temporal and cellular hippocampal expression pattern of two seizure-sensitive calcium-binding proteins, calbindin-D-28k and calretinin, in GABA(B(1))(-/-) mice. One month after birth, before the onset of overt epileptiform activity, wild-type (WT) and GABA(B(1))(-/-) mice exhibit comparable expression profiles for the two calcium-binding proteins. Three months after birth, once the epileptic phenotype is established, we observe clear alterations in the expression of calcium-binding proteins in the dentate gyrus area. GABA(B(1))(-/-) mice exhibit a 50% decline in the staining intensity of calbindin-D-28k expressing neurons and a 70% increase in the number of calretinin-positive neurons when compared to WT littermates. Six months after birth, the down-regulation of calbindin-D-28k protein is even more pronounced, while the calretinin expression in GABA(B(1))(-/-) mice reverts to the pattern seen in WT littermates. Our data demonstrate that the absence of functional GABA(B) receptors causes epileptiform activity through a mechanism that crucially involves dentate gyrus granule cells, and that this pathological activity is accompanied by adaptive changes.

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