SHORT COMMUNICATION

TNAP IN THE BRAIN: FUNCTIONS IN NEUROTRANSMISSION

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Alkaline Phosphatase (AP) activity has been found within the brain tissue of many mammalian species. Using histochemistry, we described a highly specific regional and laminar distribution of AP activity in the cerebral cortex of both human and non-human primates. Notably, AP activity was extracellularly localized in the synaptic cleft and at the nodes of Ranvier. It was also found to be regulated by neuronal activity as shown by our sensory deprivation experiments. Moreover AP activity was regulated during postnatal development. These findings strongly suggest that AP is involved in neurotransmission and cerebral cortex functions. This hypothesis, in view of the neurological symptoms accompanying human Tissue-Nonspecific Alkaline Phosphatase (TNAP) deficiencies (epilepsy), deserved to be tested. We first aimed at testing whether AP activity in the normal cerebral tissue could be attributed to TNAP gene expression rather than to other APs. Using PCR we have not found any brain specific transcripts. Neurons express the bone TNAP transcripts, except in mouse, where they also express the liver TNAP transcripts. To tackle the functions of TNAP in the brain, we used the TNAP-KO mice (Akp2-/-) model that mimics the severe form of human hypophosphatasia, including epilepsy. Ultrastructural analyses showed intense cellular degradation in the oligodendroglia processes of the paranodal region and a hampered cortical synaptogenesis. HPLC studies indicated that the concentration of GABA was markedly reduced and that of serine and glutamate slightly decreased in the Akp2-/- mice. Alterations in the behaviour of KO pups, which do not survive beyond the tenth postnatal day, were subtle but indicated a delayed maturation of the sensory motor responses. In adult mice, absence of one allele (Akp2+/-) resulted in higher anxiety and in contextual memory impairment. Electrophysiological recording in slices of mouse somatosensory cortex maintained in vitro was used to investigate the putative role of TNAP in controlling synaptic transmission. Blocking TNAP activity with tetramisol elevated evoked potential amplitude and modified patterns of chemicallyinduced seizure activity. Tetramisol also modified short-term synaptic plasticity, significantly reducing synaptic depression. These electrophysiological data are compatible with the putative roles of TNAP in regulating GABA synthesis and extracellular adenosine concentration. Altogether, our results strengthen an essential role of TNAP in the development and maintenance of normal neurotransmission in the brain.

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