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Abstract

Network Abnormalities Detected In Vitro in a Down Syndrome Model Mouse

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Epilepsy is a common co-morbidity in syndromes that affect learning and cognition. In Down syndrome (DS; trisomy 21) – the most common cause of non-inherited learning disability – epilepsy affects 5-15% of the population, compared to < 1% in the general population. The DS model mouse Ts65Dn (chromosome 16 segmental trisomy) exhibits audiogenic seizures, deficits in hippocampal-dependent behaviors, and altered long-term synaptic plasticity.
We studied the properties of CA3 neurons in hippocampal slices isolated from Ts65Dn mice (4-8 months). Spontaneous synchronized, short (interictal-like) bursts were recorded in Ts65Dn slices, whereas no spontaneous synchronized activity was observed in slices from control mice. Disinhibition by the $GABA_A$ receptor antagonist bicuculline – which induced interictal-like bursts in control slices – caused also the appearance of synchronized prolonged (ictal-like) discharges in Ts65Dn slices. These discharges were reduced in duration by group I metabotropic glutamate receptor (mGluR) antagonists.
In vivo high spatial resolution fMRI maps revealed higher cerebral blood volume (CBV) in the CA3 region of Ts65Dn mice compared to control. In 60-80% of the slices isolated from the same Ts65Dn mice, spontaneous interictal-like bursts were recorded in CA3. In contrast, in 2-month-old mice, hippocampal CBV values of Ts65Dn mice were not different from those of control mice. Only 14% of the Ts65Dn slices from the same animals showed interictal-like bursts.
Thus, altered mGluR-mediated synaptic responses may contribute to epilepsy and the impairment of brain functions in DS. Also, a phase of abnormally high metabolism and excitability in the hippocampus may precede the Alzheimer's disease-like pathophysiology observed in DS.