Astrocyte-dependent susceptibility to excitotoxicity in spermine oxidase overexpressing mouse

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The complex functions of polyamines in mammalian brain were investigated by using a new transgenic mouse model overexpressing spermine oxidase in the cerebral cortex neurons (Dach-SMO mouse), which shows increased susceptibility to kainate-induced excitotoxicity and epileptic seizures. To better understand the mechanisms involved, we evaluated: i) the neuron loss and astrocyte proliferation using specific markers in immunohistochemistry and Western Blot analysis; ii) the ability of kainate to evoke glutamate release from cerebral cortex purified nerve terminals and astrocyte processes in superfusion experiments; iii) the possible role of astrocytes in the seizure susceptibility using an *in vitro* model of epileptic-like activity in combined hippocampus-neocortex slices recorded with a multi-electrode array (MEA) device; iv) the oxidative status of the cerebral cortex of both Dach-SMO and control mice by evaluating antioxidant defense (superoxide dismutase, catalase and metallothioneins).

In the cerebral cortex of SMO-overexpressing mice we observed: i) an increased number of astrocytes showing morphological features typical of reactive astrogliosis and a loss of neurons; a marked astrogliosis was confirmed by relative abundance of astrocyte processes with respect to the nerve terminals; ii) the ability of kainate to evoke release of the gliotransmitter glutamate in purified astrocyte processes prepared only from Dach-SMO mice; the pharmacological characterization indicated that the response to kainate was accounted for by AMPA receptors including Ca^{2+}-permeable GluA2-lacking receptors; iii) an increased susceptibility to kainate-evoked cortical epileptogenic activity, dependent on astrocyte function; iv) an increased oxidative stress and activation of defense mechanisms involving both neurons and astrocytes.

We conclude that in the mouse model with a deregulated polyamine metabolism, the increased reactive oxygen species production in both astrocytes and neurons, the reactive astrocytosis and the activation of glutamate release from astrocyte processes might be involved in the susceptibility to kainate excitotoxicity. In fact, taken together our findings suggest that as a consequence of spermine oxidase overexpression, reactive astrocyte activation, with astrocyte processes expressing functional Ca^{2+}-permeable AMPA receptors, might contribute to a secondary cascade of glutamate release that could increase the brain vulnerability to kainate excitotoxicity, worsened by the increased reactive oxygen species production. This model would help to shed light on roles for astrocytes in increasing vulnerability to excitotoxic neuron injury.

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