System $x_c^-$ activity determines extracellular hippocampal and striatal glutamate levels: implications for neurological disorders associated with excessive glutamate release

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Introduction

Malfunctioning of the cysteine/glutamate antiporter or the so-called system $x_c^-$, responsible for exchanging intracellular glutamate for extracellular cysteine, can cause oxidative stress as well as excitotoxicity, important phenomena in the pathogenesis of Parkinson’s disease and epilepsy [1].

Methods

We used mice lacking xCT (xCT−/− mice), the specific subunit of system $x_c^-$, to study in vivo the effect of system $x_c$ deficiency on striatal and hippocampal glutathione content and extracellular glutamate concentrations. Next, we investigated the sensitivity of xCT−/− mice for a Parkinson’s disease inducing toxin (6-hydroxydopamine, 6-OHDA) as well as for various chemoconvulsants evoking limbic seizures.

Results and Discussion

Although cysteine imported via system $x_c$ is intracellularly reduced to cysteine, the rate-limiting substrate in glutathione synthesis, deletion of xCT did not affect striatal or hippocampal glutathione levels. Accordingly, no signs of increased oxidative stress were seen in xCT−/− mice. However, extracellular hippocampal and striatal glutamate levels were decreased with >60% in xCT−/− mice compared to controls. In addition, intrahippocampal perfusion with system $x_c$ inhibitors lowered extracellular glutamate whereas the system $x_c$ activator N-acetylcysteine elevated extracellular glutamate in the rat hippocampus. This indicates that
system $x_c^-$ may be an interesting target for pathologies associated with excessive extracellular glutamate release. Correspondingly, xCT deletion in mice elevated the threshold for limbic seizures and abolished the proconvulsive effects of N-acetylcysteine [2]. Moreover, in sharp contrast to the expectations, xCT$^{-/-}$ mice were less susceptible to 6-OHDA-induced neurodegeneration in substantia nigra pars compacta compared to wildtype littermates [3].

The current data sustain that system $x_c^-$ is an important source of hippocampal and striatal extracellular glutamate and an innovative target for the future development of antiepileptic and/or neuroprotective drugs.

References

