Arginine metabolism and the exceptional resistance of hippocampal CA2 neurons to damage under excitotoxic conditions

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Aim. The hippocampus is responsible primarily for memory and is made of dentate gyrus (DG) and cornu ammonis (CA), the latter divided into CA1, CA2 and CA3. In comparison with other hippocampal regions, neurons of the CA2 are characterized by unique properties, including high resistance to damage. The molecular basis behind this phenomenon is not understood. The aim of this study was to verify the direction of arginine metabolism in CA2 and its importance for the specific properties of this region neurons.
Methods. The distribution of proteins associated with arginine metabolism was analyzed in the hippocampus of wild-type mice using immunofluorescent staining. The role of the arginine metabolism pathway in protection against neuronal damage was studied in a pharmacological model of excitotoxicity (NMDA), using organotypic cultures of hippocampal slices from 7-day-old Wistar rats.
Results. I have found that the CA2 region of the hippocampus is characterized by a unique profile of gene expression related to arginine metabolism. Proteins involved in the conversion of arginine to polyamines (PAs), namely arginase 2, ornithine decarboxylase, spermidine synthase, and spermine synthase, were significantly enriched in CA2 pyramidal neurons while being absent or expressed at much lower levels in CA1 and CA3. Additionally, the expression of the neuronal form of nitric oxide synthase, an enzyme catalyzing a reaction competitive to PAs synthesis - the production of nitric oxide from arginine, was significantly reduced in CA2 compared with CA1 and CA3. Inhibition of PAs synthesis, using DFMO, in an organotypic model of hippocampal excitotoxicity resulted in sensitization of CA2 pyramidal neurons to the toxic effects of NMDA, when, in contrast to CA1 and CA3, this region displayed high resistance to NMDA exposure in the absence of DFMO.
Conclusions. Our data strongly suggest a differential direction of arginine metabolic pathways in individual regions of the hippocampus. Specific enrichment of PAs synthesis in the CA2 may be a key factor for the special resistance of neurons of this region to excitotoxicity.

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