Investigation of the Role of Free-Radical Processes in Epilepsy and Epileptogenesis

I. V. Gusakov, A. G. Golubev, and D. K. Kambarova

Institute of Experimental Medicine, Russian Academy of Medical Sciences, St. Petersburg

Numerous disturbances of cerebral function, including Parkinson's disease, Alzheimer's disease, insults, and epilepsy, are linked to the intensification of free-radical processes. However, it is not clear whether this is a nonspecific epiphenomenon or a factor in the development of specific symptoms. In order to answer this question, it is appropriate to study the effects of specific inhibitors of the corresponding processes on the development of disease symptoms.

We studied the effect of intravenous injections of superoxide dismutase (SOD) and Olifen, a novel antihypoxant with an antioxidant activity (both preparations produced at the Institute of General and Specific Biochemistry, St. Petersburg), on seizures after kindling of the amygdala and the effect of the Fe chelator Desferal on the development of post-trauma epilepsy induced by subdural injection of autologous blood in the rat. It was found that SOD alleviates seizure activity in the 5th stage of epilepsy, inhibits spontaneous and electrostimulated electrographic manifestations of seizures, and raises the threshold values of the stimulating current. Olifen elicited similar effect with specific time- and dose-dependence. Neither SOD nor Olifen was effective in the corazole or electric shock model of epilepsy. Intramuscular injections of Desferal resulted in a decrease in Fe content at the site of blood injection and inhibited the development of an epileptic focus.

Since in this model Fe catalyzes lipid peroxidation, the results obtained confirm the ability of free-radicals to cause damage to nervous tissue, which leads to the development of epilepsy. Concerning the effects of antioxidants after the formation of an epileptic focus, the results obtained in experiments with different antioxidants and different models are controversial, indicating the importance of a specific target for each preparation in the generation of seizure activity. Superoxide radical is the target for SOD. This radical is not only involved in LPO activation but also inactivates nitrogen oxide. The significance of the latter in the development of seizure activity is unknown and is the subject of our current studies.

The Glutamate Receptor System in the Mechanism of L-Arginine-Dependent Generation of Nitrogen Oxide

N. Gorbunov

I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, St. Petersburg

It is known that in cells of the central nervous system (CNS) nitrogen oxide (NO) is generated from L-arginine due to the activation of Ca-calmodulin-dependent nitrogen oxide synthetase (NOS), increased Ca permeability of the plasma membrane, or mobilization of intracellular Ca. These mechanisms may be triggered by stimulation of the glutamate receptors (GR), which play an important role in synaptic transduction in cerebellar neurons.

The role of NMDA- and AMPA-cainate ionotropic and metabotropic GR in the mechanism of NOS activation was studied in the subcellular synaptosome fraction (SpF) isolated from the rat cerebellum. It was demonstrated that the baseline NOS activity in SpF was dependent on the presence of exogenous NADPH and L-arginine. Stimulation of the glutamate receptors by NMDA increased NO production. The increase was dependent on the presence of extracellular Ca and was abolished by the antagonist AP-5, while the stimulation of GR by AMPA did not increase NOS activity. The agonist of the metabotropic GR ACPD and glutamate increased the NO content in SpF, which did not depend on the presence of extracellular Ca. The effect of ACPD and glutamate in the absence of extracellular Ca was abolished by the antagonist AP-4, the inhibitor of the inositol triphosphate receptors of calcitosomes dantrolene, or the calmodulin inhibitor W7. These data demonstrate the significance of metabotropic GR in the regulation of L-arginine-dependent NO synthesis in the cerebellar neurons.