Editorial

The cerebral cortex is exquisitely sensitive to hypoxia with relatively moderate reductions in O_2 tension resulting in a spectrum of central nervous system–related symptoms ranging from impairment of higher cognitive functions to complete silencing of the electroencephalogram (1, 2). An obvious issue in interpreting this loss of neuronal activity is whether neuronal failure is caused by a limitation of energy substrates or is an adaptive process of neurons to reduce metabolism in the face of limited oxygen supply. Reducing neuronal metabolism by stabilizing membrane potential and decreasing the production of action potentials would provide the brain with a process designed to limit the use of metabolic substrates to that necessary for maintenance of cellular integrity and thus extend the time to which neurons can be exposed to hypoxia without resultant cellular damage. The elegant study by Cummins et al. (3) in this issue of *The Journal* makes a strong case that this strategy is employed by human cortical neurons during anoxia.

But how is this adaptive strategy implemented? Studies of hypoxia in vivo and in vitro have suggested two major mechanisms, short of depolarization blockage, for reducing neuronal membrane excitability. First, there is evidence that changes in the metabolism, release, and/or reuptake of both excitatory and inhibitory neuroeffectors produce an increased extracellular concentration of inhibitory neuromodulators (for review, see reference 4). At the same time, direct effects of anoxia on the membrane conductance of potassium have been correlated with reductions in postsynaptic excitability of hippocampal neurons (5). The study by Cummins et al. (3) demonstrates that a reduction in sodium conductance is also an important factor in reducing excitability of cortical neurons during anoxia. It is interesting that both the potassium and sodium channel effects seem to be dependent on ATP. While a decrease in ATP during hypoxia seems obvious, previous studies (6) were unable to detect any reduction in the levels of high energy phosphates in the cortex even with severe hypoxia. This observation has been challenged by Lipton and Whittingham (5) who found localized reductions in ATP levels in synaptic regions of the hippocampus during anoxia, suggesting an activity-dependent loss of ATP and a feedback mechanism capable of modifying potassium conductance to reduce activity. Thus, the proposal by Cummins et al. (3) that the change in sodium inactivation during anoxia is linked to cellular metabolism through decreases in ATP would provide a reasonable mechanism for mediating reductions in neuronal excitability during anoxia. It is likely that, in conjunction with enhanced inhibitory neuromodulation and reductions in potassium conductance, a diminished sodium current during hypoxia is another important mechanism involved in mediating depression of neuronal activity in the intact nervous system.

The physiological and clinical relevance of reduced neuronal excitability during hypoxia can not be overstated. The key to surviving the detrimental effects of hypoxia is critically linked to an ability to maintain the integrity of transmembrane ionic gradients (7). Cellular metabolic mechanisms that promote membrane hyperpolarization, reductions in ionic conductance, and a decrease in basal activity, will minimize the effect of hypoxia at the cellular level. Ultimately, this reduction in neuronal metabolism might subserve a protective function by limiting motor activity and thus preserving O_2 stores in the whole organism. This survival strategy has been proposed to take place even in the brain stem neurons involved in generating respiration (4), suggesting that neuronal survival is of the highest priority.

Judith A. Neubauer
University of Medicine & Dentistry of New Jersey
Robert Wood Johnson Medical School

References

1. Siesjo, B. K., H. Johannsson, B. Ljungren, and K. Norberg. 1974. Brain dysfunction in cerebral hypoxia and ischemia. *In* Brain Dysfunction in Metabolic Disorders. F. Plum, editor. Raven Press, Ltd., New York. 75–112.

2. Mayevskey, A., and B. Chance. 1975. Metabolic responses of the awake cerebral cortex to anoxic hypoxia, spreading depression and epileptiform activity. *Brain Res.* 98:149–165.

3. Cummins, T. R., C. Jiang, and G. G. Haddad. 1993. Human neocortical excitability is decreased during anoxia via sodium channel modulation. *J. Clin. Invest.* 91:608–615.

4. Neubauer, J. A., J. E. Melton, and N. H. Edelman. 1990. Modulation of respiration during brain hypoxia. *J. Appl. Physiol.* 68:441–451.

5. Lipton, P., and T. S. Whittingham. 1982. Reduced ATP concentration as a basis for synaptic transmission failure during hypoxia in the in vitro guinea-pig hippocampus. *J. Physiol.* 325:51–65.

6. Duffy, T. E., S. R. Nelson, and O. H. Lowry. 1972. Cerebral carbohydrate metabolism during acute hypoxia and recovery. *J. Neurochem.* 19:959–977.

7. Hochachka, P. W. 1985. Defense strategies against hypoxia and hypothermia. *Science (Wash. DC).* 231:234–241.

J. Clin. Invest.

0021-9738/93/02/0377/01 $2.00
Volume 91, February 1993, 377