

Editorial Views

On Brain Power

THE MARKED EFFECTS of anesthetics on the central nervous system emphasize the need for detailed information concerning cerebral energy production and utilization during anesthesia. Moreover, since cerebral hemodynamics and metabolism are profoundly affected by such variables as P_{aCO_2} , temperature, and hemoglobin concentration, the entire anesthetic experience must be considered. The paper by Michenfelder, Van Dyke, and Theye appearing in this issue of ANESTHESIOLOGY represents an additional contribution to this important area.

Before considering the information presented, it seems wise to review some basic aspects of cerebral biochemistry. The energy source for cerebral function is adenosine triphosphate (ATP). This important substance is produced by the phosphorylation of adenosine diphosphate (ADP), an energy-consuming process. The energy required for ATP synthesis by cerebral tissue is supplied through metabolism of glucose via anaerobic (Embden-Meyerhof glycolytic) and aerobic (Krebs citric acid cycle) pathways. ATP may also be synthesized by operation of the creatine phosphokinase reaction (creatine phosphate + ADP \rightarrow creatine + ATP) as well as through the action of adenylic kinase (myokinase) (2 ADP \rightarrow ATP + AMP). Finally, when activity of the citric acid cycle is reduced by interference with oxygen supply, increased glycolysis can temporarily maintain energy stores. Activation of glycolysis results in an increased ratio of cytoplasmic NADH/NAD⁺, an elevated lactate concentration, and an increased lactate/pyruvate (L/P) ratio.

Changes in cerebral metabolite concentrations resulting from hypoxia have been well documented,¹⁻³ and can be divided into stages depending on severity. The earliest stage of increased glycolysis is characterized by increases in lactate concentration and of L/P ratio. This direct effect of tissue hypoxia represents a metabolic compensation since anaerobic glycolysis can supply limited amounts of ATP. If the degree of hypoxia does not exceed the ability of this system to supply high-energy phosphate, no further changes are observed. During the first moments of more profound hypoxia, ATP concentration remains constant while creatine phosphate is decreased. When creatine phosphate stores are unavailable, a reduction in ATP becomes evident.

Let us now turn to an examination of the significant findings of the report of Michenfelder *et al.* Although there was a twofold variation in cerebral metabolic requirements (*i.e.*, cerebral oxygen uptake) during administration of a number of different anesthetics, ATP, lactate, and pyruvate concentrations were unchanged. Decreased metabolic need during hypothermia was characterized by reduction in cerebral oxygen utilization without alteration in the content of these three metabolites. Biopsies were performed every two minutes; two to six specimens were obtained from each dog. The passage of this short time appeared to exert no effect, indicating that the rates of ATP synthesis and degradation were equal. Thus, the anesthetized brain appears to be able to maintain energy supplies at a rate commensurate with metabolic requirements. Furthermore, the unchanged lactate

and pyruvate concentrations signify that whatever the rate of mitochondrial respiration, oxidative phosphorylation was adequate and increased glycolytic flux, therefore, was not required.

These findings do not necessarily indicate that anesthetics offer protection against cerebral hypoxia. Indeed, as the authors have pointed out,⁴ a decrease in cerebral oxygen uptake during anesthesia represents only the metabolic consequences of diminished cerebral function. On the other hand, the oxygen uptake necessary to maintain viability of brain cells is probably *unchanged* by anesthesia.

Although anesthesia did not appear to restrict cerebral oxygenation, the situation is markedly different when hyperventilation is imposed. The authors offer additional evidence that the decreased cerebral blood flow and increased hemoglobin-oxygen affinity (Bohr effect) produced by profound hypocarbia ($P_{aCO_2} = 10$ torr) can compromise cerebral oxygenation. Although the statistical methods used were not the most appropriate (analysis of variance would have been more suitable), it would appear that hypocapnia diminished cerebral ATP content, increased cerebral lactate concentration and the L/P ratio, while cerebral oxygen utilization remained normal. These findings were exaggerated by the combination of hypocapnia and anemia, which also served to diminish cerebral oxygen uptake. These changes in lactate and in the L/P ratio signify the presence of increased glycolysis and reduction of the NADH/NAD⁺ system, an observation confirmed by others.^{5,6} The significance of the small changes in ATP concentration, not noted by Granholm and Siesjö during less severe hypocarbia in the cat ($P_{aCO_2} = 17$ torr),⁵ is more difficult to assess. As previously mentioned, ATP concentration may show slight changes at a time when serious interference with energy production is evidenced by decreased creatine phosphate and increased AMP. Thus, the full impact of oxygen lack may not be realized without measurement of ATP, AMP, and creatine phosphate. Furthermore, since significant cerebral hypoxia results in progressive changes in the concentrations of these metabolites, it is important to document the effects of time. A stable level would indi-

cate a new steady state at which energy synthesis and utilization were again equal. Finally, since the electroencephalogram was unchanged at a time when ATP levels were further diminished by superimposition of anemia upon hypocarbia, the relationship of these changes to a "critical" level of ATP remains to be determined.

In conclusion, the authors have provided two important items of information: 1) when anesthesia is considered alone, cerebral energy production is matched to energy utilization; 2) tissue hypoxia resulting from extreme hypocapnia is accompanied by reduction of the NADH/NAD⁺ system and increased glycolysis. The observation of altered ATP concentrations may indicate that the metabolic compensation inherent in increased glycolysis is insufficient. The effect of time, measurements of other significant metabolites, and the determination of a "critical" level of ATP concentration in this experimental model remain to be explored.

PETER J. COHEN, M.D.

Professor and Chairman

Department of Anesthesia

*University of Colorado Medical Center
Denver, Colorado*

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