This Week's Citation Classic®

Lowry O H, Passonneau J V, Hasselberger F X & Schulz D W. Effect of ischemia on known substrates and cofactors of the glycolytic pathway in brain.
J. Biol. Chem. 239:18-30, 1964.
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Mouse brains were analyzed for all known metabolites and cofactors on the Embden-Meyerhof pathway after total ischemia lasting from four seconds to 20 minutes. The results showed a sevenfold increase in flux along the pathway associated with sequential activation of phosphofructokinase, hexokinase, and phosphorylase. [The *SCI*® indicates that this paper has been cited in over 1,830 publications.]

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April 10, 1987

The control of metabolic systems in general and of glycolysis in particular has been of concern since the time of Louis Pasteur. But in the late 1950s and early 1960s this interest increased as the potential mechanisms of control became better known and better tools for their study were developed.

About this time, Janet Passonneau and I were trying to get into the field and had in fact described some results on control of brain phosphofructokinase.[1] We therefore decided to undertake an extreme case and an ambitious goal: to determine the effects of total ischemia on every mouse brain metabolite and cofactor on the path from glycogen and glucose to lactate.

Naturally, we went all out to elaborate satisfactory methods and to work out a convenient way to prepare brain extracts as free as possible of artifacts. Unambiguous ischemia was produced by decapitation, and the heads were frozen after eight intervals from four seconds to 20 minutes. Adult and 10-day-old mice were used, both anesthetized and unanesthetized.

Shutting off the blood supply converted the brain into a closed biological system, limited the chemical events to those that can occur without oxygen, and abruptly increased by sevenfold glycolysis plus glycogenolysis. At issue were the mechanisms that control and decontrol glucose and glycogen brain metabolism. We wanted to know what the control points are and how ischemia turns them on.

The metabolite changes and their time courses clearly confirmed previous evidence for three major control steps: those catalyzed by hexokinase, by phosphorylase, and by phosphofructokinase. However, they furthered our knowledge by indicating that there was little control elsewhere on the pathway to lactate. The results also indicated that the primary control event was activation and deinhibition of phosphofructokinase (rapid increase in fructose bisphosphate and fall in glucose-6-phosphate) apparently caused by the initial increases in ADP, AMP, and P_i, and decrease in ATP. Activation of hexokinase and phosphorylase (decrease in glucose and glycogen) were clearly delayed and probably could be attributed in part to a combination of the fall in glucose-6-P and the rise in P_i.

I would guess that the reason this paper has been frequently cited is that it had a little something for everyone, or at least for those interested in brain metabolism, a group that has been growing since 1964. The paper also had quite a few least-publishable units. The methods section alone ran to over five pages in the *Journal of Biological Chemistry* with detailed, somewhat novel procedures and increased sensitivities for 20 metabolites. A sampling of the papers that cited our article suggests that about half the authors were interested in our brain data and the other half in our methods. It intrigued us to discover that over the years the proportions have shifted from a slightly greater interest in the methods to a twofold greater interest in the metabolic results. In retrospect, it was a lot of work for the four of us, but we believe it was worth it. [For a recent discussion of this subject, see reference 2.]

1. **Passonneau J V.** Phosphofructokinase and the Pasteur effect. *Biochem. Biophys. Res. Commun.* 7:10-5, 1962. (Cited 510 times.)
2. **Hansen A J.** Effect of anoxia on ion distribution in the brain. *Physiol. Rev.* 65:101-48, 1985.

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