COMPUTER SIMULATION OF METABOLISM IN PALMITATE-PERFUSED RAT HEART. I. PALMITATE OXIDATION

Michael C. Kohn†
David Garfinkel

Department of Computer and Information Science
Moore School of Electrical Engineering
University of Pennsylvania
Philadelphia, Pennsylvania

A computer model of the fatty acid oxidation pathway in perfused rat heart was constructed. It includes uptake, activation, and \( \beta \)-oxidation of fatty acids, triglyceride synthesis and hydrolysis, and carnitine-dependent transport of acyl groups across the mitochondrial membrane under pseudosteady state conditions. Fatty acid utilization may be limited by \( \beta \)-oxidation in hypoxia or ischemia but probably not in aerobic conditions. Nonesterified fatty acids bound to proteins are found to be metabolically available. The model predicts that stearate, but not palmitate, can support the highest observed respiration rate for perfused rat heart without supplementation by other substrates. Fatty acids are preferentially oxidized rather than being stored as triglycerides because the cytosolic acyl CoA level is lower than the \( K_m \) for triglyceride synthesis. It is suggested that feedback inhibition of triglyceride lipase regulates utilization of triglycerides as fuel in aerobic hearts.

Keywords — Enzymes, Simulation, Fatty acid metabolism, Metabolic regulation.

Previous simulation of cardiac metabolism (1,29) predicted transient utilization of endogenous triglycerides as metabolic fuel for the aerobic perfused rat heart under a variety of conditions. However, the contribution of fatty acid metabolism to respiration was only crudely represented in these models. A large literature now exists on the possible deleterious effects of long-chain acyl intermediates in ischemic heart (52). Because of its importance in both normal

Supported by NIH grant HL 15622.
†Present address: Dept. of Physiology, Duke University Medical Center, Durham, NC 27710.
Reprint requests to: D. Garfinkel, Moore School of Electrical Engineering, University of Pennsylvania, Philadelphia, PA 19104.

361
and pathological conditions, we have modeled the fatty acid metabolic pathway in detail and combined the result with an updated model of the area of cardiac metabolism previously simulated.

Because fatty acid metabolism has been less thoroughly studied than the metabolism we previously modeled, we have had to draw inferences from incomplete data or from data obtained from other mammalian tissues. All of these inferences are justified in the following text. When no information exists regarding some process, any assumptions necessary to permit modeling that process were made so that they had little or no effect on the behavior of the complete model. The purpose of our modeling is not merely to replicate or mimic reality (especially where our knowledge of reality is incomplete) but to test the plausibility of hypotheses regarding the properties of a metabolic pathway and to help design new experiments to answer unresolved questions.

In this paper we report the construction of “submodels” (see below) of the individual enzymes of this pathway. Since the total amount of available information regarding the submodels exceeds that available for the whole-heart preparation being modeled, construction of submodels entails most of the work of model construction; subsequent assembly of the submodels into a unified model and identification of parameter values is a much less time-consuming task. We show that our mathematical description of the fatty acid metabolic pathway reproduces known properties and behavior of the pathway in the perfused rat heart. In the following paper (31) we report the incorporation of these submodels into an updated version of an existing model of cardiac intermediary metabolism to examine how they behave as part of a larger system. For this purpose we simulated a Langendorff rat heart preparation perfused with glucose- and palmitate-containing buffer (44,45,53) which is biochemically the most physiological of all those we have simulated. Sensitivity analysis of the complete model was then performed to identify the processes which most strongly regulate utilization of endogenous and exogenous fuels in this preparation.

**STRATEGY OF MODEL CONSTRUCTION**

Although our modeling techniques have been described elsewhere (19), a brief review would help the reader follow the often complex reasoning involved in this work. Our computer model of the perfused rat heart consists of a sequence of chemical equations representing the catalytic mechanisms of all enzymes and all nonenzymatic reactions (e.g., nucleotide chelation equilibria) in the model. The reaction sequence for a particular enzyme constitutes the “submodel” for that enzyme. Our simulation program translates these chemical equations into reaction rate laws, which are evaluated for the physiological state being modeled. The time derivative of a metabolite concentration is given by a linear combination of rate laws in the computer program. Conservation of mass is thus obeyed.