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Integrating Cellular Metabolic Processes to Whole-Body Metabolism

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Cellular metabolic processes are regulated at the level of individual enzymes and participating chemical species. However, the significance of specific enzymes on individual metabolic pathways and their regulation must be viewed in the context of the whole organism. A complete knowledge of the structure and dynamics of the individual components of this multi-level metabolic network is not sufficient to understand human metabolism and its regulation. To determine the significance of molecular events and their contribution to control of metabolic processes and regulation of metabolism at the tissue/organ and organism levels, these levels of complexity must be linked together.

Currently, we are applying a Multi-level Systems Analysis (MSA) approach to model metabolic dynamics at various levels of biological complexity (cellular, organ/tissue, organism) by integrating metabolic pathways and tissue/organs interactions. This integrated MSA modeling approach is based on mass balances in a physiological framework. Resulting systems of nonlinear differential equations representing metabolism in brain, heart, liver and skeletal muscle, are numerically integrated to simulate the effects of hypoxia, exercise, diet, and drugs on organ and whole body metabolism. Computer simulations of organ responses to the above stressors are then compared to experimental data from in vivo animal or human studies under corresponding conditions for model validation and improvement. The mechanistic modeling approach used to test hypotheses in complex metabolic networks is the main objective of a newly created Center for Modeling Integrated Metabolic Systems (MIMS) funded by the National Institute of General Medical Sciences of NIH. These models provide an excellent tool to integrate biochemical, cellular, and tissue/organ data, as well as a physiological framework for analysis and interpretation of metabolic responses to stress.

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