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A systemic approach to explore the flexibility of energy stores at the cellular scale: Examples from muscle cells

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HIGHLIGHTS

- The influence of challenges on the dynamic of cell energy stores is modeled.
- Studied challenges are variations in eating frequency, physical activity and cell characteristics.
- The model illustrates the role of the energy stores flexibility on a muscle cell adaptation.
- Sensitivity analysis based on Sobol method highlighted the important parameters.
- These parameters are glycogen maximum accumulation capacity and homeostatic energy demand.

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ABSTRACT

Variations in energy storage and expenditure are key elements for animals adaptation to rapidly changing environments. Because of the multiplicity of metabolic pathways, metabolic crossroads and interactions between anabolic and catabolic processes within and between different cells, the flexibility of energy stores in animal cells is difficult to describe by simple verbal, textual or graphic terms.

We propose a mathematical model to study the influence of internal and external challenges on the dynamic behavior of energy stores and its consequence on cell energy status. The role of the flexibility of energy stores on the energy equilibrium at the cellular level is illustrated through three case studies: variation in eating frequency (i.e., glucose input), level of physical activity (i.e., ATP requirement), and changes in cell characteristics (i.e., maximum capacity of glycogen storage).

Sensitivity analysis has been performed to highlight the most relevant parameters of the model; model simulations have then been performed to illustrate how variation in these key parameters affects cellular energy balance. According to this analysis, glycogen maximum accumulation capacity and homeostatic energy demand are among the most important parameters regulating muscle cell metabolism to ensure its energy equilibrium.

1. Introduction

Living organisms need energy to sustain their basal metabolism, i.e., the physically and psychologically undisturbed state in a thermoneutral environment where basic functions of organs are ensured. Energy is also needed to ensure physical activity (movement and locomotion) and homeorhetic functions such as development, growth, or reproduction. When dietary energy intake exceeds energy expenditure, surplus energy is stored in specific cells. Both the energy supply and energy expenditure are important factors regulating the storage and mobilization of energy from the stores. Indeed, to cope with environmental constraints (e.g., intermittent feed supply, immune or inflammatory challenges, heat stress), cell metabolism has to quickly adapt new strategies to activate the chemical reactions required for cell communications, division and several other physiological processes; this can be realized due to the flexibility of different anabolic and catabolic pathways. This adaptation also has important long-term consequences on the characteristic of energy stores to anticipate homeorhetic challenges.

Animal is a complex system and its response to a perturbation is due to the coordinated response of all its subsystems and their interactions at different spatial and temporal scales. At microscopic scale, it is recognized that the flexibility of cell metabolism is due to the number of metabolic intermediates in anaerobic and aerobic pathways, the succession of different enzymes controlling the rates of chemical reactions, and the interconnection between

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metabolic pathways. Two main forms of energy storage within eukaryotic cells are glycogen and lipids. Adenosine triphosphate (*ATP*), the cellular currency of energy transfer, can be synthesized by mobilizing energy from energy stores or by taking up circulating energy-yielding nutrients. Different cells within a tissue may also interact to exchange nutrients and transfer energy. To date, different models of energy metabolism in many systems from cellular scales to animals have been proposed to investigate specific questions (Baldwin et al., 1976; Sauvant, 1992; Hanigan and Baldwin, 1994; van Milgen et al., 2008; Martin and Sauvant, 2010). To our knowledge, these models do not specifically describe the dynamic balance between glycogen stores and lipid stores within the same cell.

Different methods exist to model the cell metabolism. Topological analysis and flux balance analysis have been used to describe metabolism based on static approaches (Jeong et al., 2000; Wagner and Fell, 2001; Blavy et al., 2014; Abdou-Arbi et al., 2014). At the cellular scale, the main metabolic pathways have been notably integrated into a generic stoichiometric model by our group (van Milgen, 2002). This framework is based on carbon chain pivots and cofactors involved in stoechiometric equations and allows quantifying catabolic and anabolic reactions. However, to describe the dynamic balance of energy stores at the cellular scale, dynamic models are likely more appropriate. Kinetic approaches to model the dynamics of biochemical reactions are generally based on ordinary differential equations or stochastic processes.

The use of the latter approach for studying the metabolism of farm animals, for which adaptation to environmental perturbations is of a main interest for the efficiency and sustainability of agricultural systems, was notably pioneered by Baldwin et al. (1976), Sauvant (1992) and Hanigan and Baldwin (1994). Also, other studies have been published (Heinrich et al., 1977; Steuer, 2007; Cloutier et al., 2007; Ghorbaniaghdam et al., 2012; Cornish-Bowden, 2008), using a limited number of variables and pathways (e.g., glycolysis) represented in a simplified way (de Atauri et al., 1999). A prerequisite when trying to understand the flexibility of energy stores in mammalian cells is to represent glycolytic and oxidative pathways together with branched pathways for lipid or glycogen syntheses (Ghorbaniaghdam et al., 2012) and their respective hierarchy in the fed and fasted states, while taking into account intra-cellular and extra-cellular signals.

Skeletal muscle is a major tissue where insulin stimulates glucose uptake from the blood. Skeletal muscle cells are the cells that use the majority of energy to sustain contraction during exercise, and are able to store energy in different forms. Two major muscle cells can be distinguished, (i) fast-twitch glycolytic fibers having high levels of stored glycogen with the enzymes necessary for producing energy without oxygen and high ATPase activity, and (ii) slow-twitch oxidative fibers that primarily release on mitochondrial fatty acids oxidation to produce ATP and can be histochemically characterized by slight staining for glycolytic capacity. The fatty acids used for energy production in muscle cells can be released from intra-myocellular triacylglycerol droplets and/or originated from lipolysis in adipocytes, providing an illustration on how different cells may also interplay during increased muscular work. Muscle cell thus represents an interesting case-study for a better understanding on how the metabolic pathways that control the balance between glycogen and lipid stores are able to adapt to internal and external stimuli.

The main objective of this work is therefore to focus on the role of glycogen and fatty acids balance to ensure energy equilibrium of a theoretical muscle cell (used as a toy model in the context of this paper) when challenged by energetic perturbations. To this end, a dynamic and mechanistic model of energy metabolism at cellular scale has been developed. The variations in the external and internal cell environments were integrated in the model to illustrate (by means of model simulations) the dynamic (time-related) metabolic adaptation for muscle cell. These perturbations consist in changes in the frequency of nutrient supply and changes in energy consumption by the cell. In addition, long term perturbations may also trigger important changes in basal cell characteristics, such as the re-orientation of substrate from glycolytic to oxidative patterns in exercising muscles. We have used the model to explore the influence of the maximum intra-cellular glycogen storage capacity as a trait affecting the metabolic behavior of myocytes.

A system of ordinary differential equations is used to represent the biochemical reactions notably located at the intersection of two or more metabolic pathways related to glycogen and fatty acids mobilization and storage, and *ATP*/*ADP* ratio is considered as the main internal regulator to switch from anabolic pathways to catabolic pathways. To highlight the key factors (model parameters) controlling fatty acids vs. glycogen balance, methods based on global sensitivity analysis are used.

The model combines existing knowledge with a new dynamic framework to investigate relevant hypotheses, such as post-prandial energy metabolism and the role of the flexibility of intracellular energy stores on the energy equilibrium at cell scale. To investigate other types of energy challenges and other cells, model parameters can further be changed and other pathways can be easily added to this simplified framework without changing its general structure.

The paper is organized as follows: in Section 2, we present the methods for model construction and exploration. Model results based on these methods are then presented in Section 3. Model properties and potential future developments are discussed in Section 4.

2. Material and method

The biochemical reactions are simplified by merging metabolic pathways of some reversible and irreversible reactions that are not limited by energy status of the cell. The simplified map of biochemical reactions of the model is represented in Fig. 1. During the simulation time frame, several biochemical reactions involved in energy metabolism are assumed to be in equilibrium (i.e., the equilibrium is established very fast compared to the simulation time scale). Therefore, there is no need to specifically represent all reactions, and some of which can be merged as irreversible reactions. This concerns the different reactions of the respiratory chain, gluconeogenesis, and ketosis. This hypothesis allows limiting the number of equations used without affecting the outcome of the simulations. Nonetheless, the *ATP* synthetized by the respiratory chain is calculated from *NADH* and $FADH_2$. A potential synthesis of oxaloacetate is also included to ensure the functioning of the *TCA* cycle (tricarboxylic acid cycle) and de novo *FA* synthesis (Table 1, for more details see Electronic Supplementary material).

Even if cell metabolism is tightly regulated by various intracellular and extra-cellular signals such as hormones, we assume in this model, that the energy equilibrium at the level of the cell is ensured only by the intrinsic cell metabolism. In this way, rather than introducing insulin as an explicit extra-cellular regulator of glucose uptake from blood (by regulation of the translocation of glucose transporters (GLUT4)), the value of the energy level in the cell (*ATP* to *ADP* ratio) regulates glucose uptake (Fig. 2).

2.1. Mathematical model formulation

A system of coupled non-linear ordinary differential equations is used to describe the flexibility of energy metabolism and the