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An old paper revisited: "A mathematical model of carbohydrate energy metabolism. Interaction between glycolysis, the Krebs cycle and the H-transporting shuttles at varying ATPases load" by V.V. Dynnik, R. Heinrich and E.E. Sel'kov

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Abstract

We revisit an old Russian paper by V.V. Dynnik, R. Heinrich and E.E. Sel'kov (1980a, b) describing: "A mathematical model of carbohydrate energy metabolism. Interaction between glycolysis, the Krebs cycle and the H-transporting shuttles at varying ATPases load". We analyse the model mathematically and calculate the control coefficients as a function of ATPase loads. We also evaluate the structure of the metabolic network in terms of elementary flux modes.

We show how this model can respond to an ATPase load as well as to the glucose supply. We also show how this simple model can help in understanding the articulation between the major blocks of energetic metabolism, i.e. glycolysis, the Krebs cycle and the H-transporting shuttles.

Keywords: Energetic metabolism; Elementary flux mode; Control coefficient; Regulation by branched structure

1. Introduction

Two years ago, we offered an Erasmus student of Reinhart Heinrich to study a simplified model of the TCA cycle during her stay in Bordeaux. Reinhart told one of us (J.P.M.) that he had developed a simple model of the TCA cycle during his stay in Pushchino with E. Sel'kov and V. Dynnik (Dynnik et al., 1980a, b and the letter, Fig. 1 in Supplementary Materials). In fact, his papers involved not only a simplified version of the Krebs cycle but also a simplification of glycolysis and of the H-transporting shuttles.

In this paper, we present the model developed by Dynnik, Heinrich and Sel'kov in the first paper (1980a, b) and interpret the results in terms of the variations of the control coefficients depending on the ATPase load. We also describe the elementary modes of the system, a concept which was not developed at that time.

2. Presentation of the model

Fig. 1 depicts the metabolic network involving glycolysis, the Krebs cycle, oxidative phosphorylation, ATP consumption and the glycerolphosphate shuttle. It reproduces the original Fig. 1 in the Russian paper with slight modifications indicated below.

Glycolysis is reduced to three reactions (reactions 1, 3 and 5): reaction 1 describes the conversion from glucose to glyceraldehyde-3-phosphate (GAP) which consumes two ATP and produces two GAP; reaction 3 contains the GAP dehydrogenase reaction that produces NADH in the cytosol ($NADH_c$) and 1,3-diphosphoglycerate (1,3-DPG); reaction 5 lumps together the remaining glycolysis reactions

Abbreviations: GAP, glyceraldhyde-3-phosphate; DAP, dihydroxyacetone phosphate; 1, 3-DPG, 1, 3-diphosphoglycerate; α-GP, α-glycerolphosphate.

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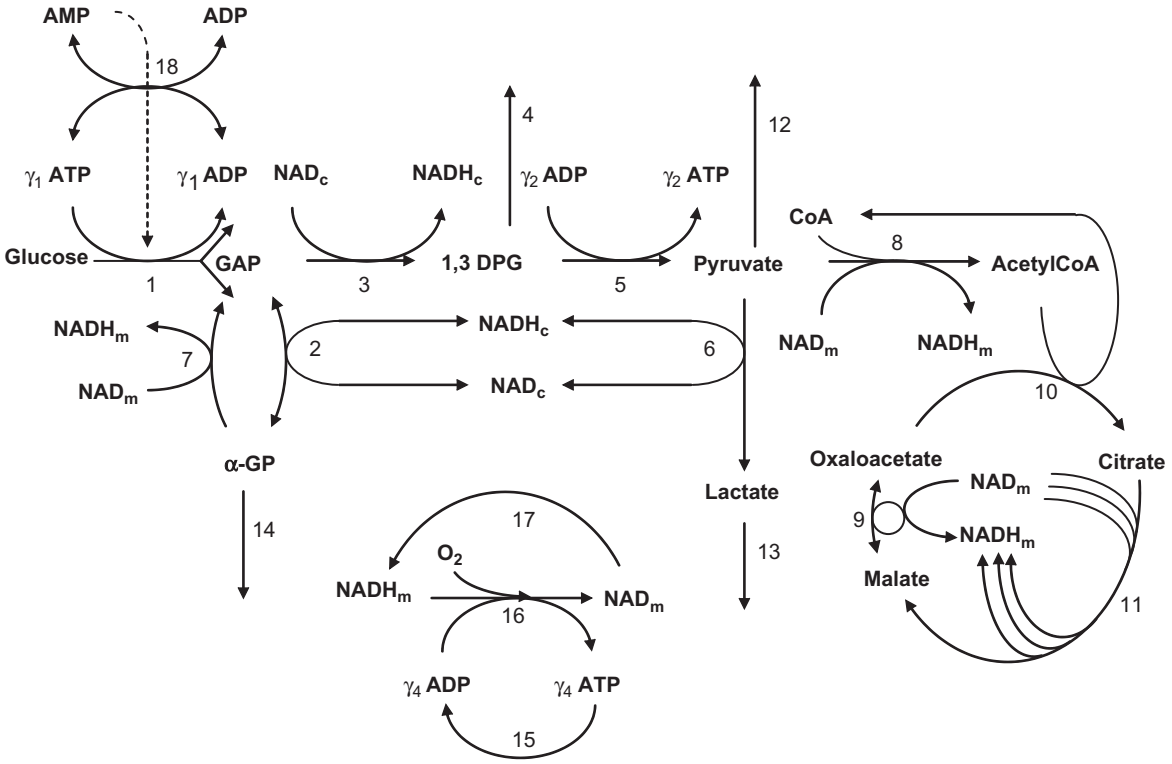

Fig. 1. Kinetic model of carbohydrate energy metabolism. 1, 3, 5 and 6: Glycolytic reactions; 2 and 7: cytoplasmic and mitochondrial α-glycerophosphate reactions of H-transporter; 8: pyruvate dehydrogenase; 9, 10 and 11: Krebs cycle; 4, 12, 13 and 14: glycolytic intermediates and α-glycerophosphate efflux; 15: total ATPase reactions; 16: oxidative phosphorylation; 17: NADH dehydrogenase; 18: adenylate kinase; dotted line: PFK activation by AMP; the indexes c and m correspond to the cytoplasmic and mitochondrial compartments. $\gamma_1 = \gamma_2 = 2$; $\gamma_3 = 3$ for NAD_m in Krebs cycle; $\gamma_4 = 3$ ATP for one $NADH_m$.

which produces two ATP molecules per GAP (four per glucose molecule) and one molecule of pyruvate (two per glucose molecule). Pyruvate can exit, be used for another metabolic pathway (reaction 12) or be converted to lactate (reactions 6) with the simultaneous reoxidation of $NADH_c$. Lactate and 1,3-DPG can also escape from the metabolic network (reactions 13 and 4, respectively).

Reaction 8 is the pyruvate dehydrogenase reaction with the production of one $NADH_m$ molecule in mitochondria. Krebs cycle is summarized in three reactions (reactions 9–11) producing four molecules of $NADH_m$. In this model, $FADH_2$ is not taken into account and replaced when necessary, as in the Krebs cycle, by a NADH molecule. The production of ATP (or GTP) by the Krebs cycle is ignored.

The conversion of $NADH_c$ to $NADH_m$ is described by the glycerolphosphate shuttle (reactions 2 and 7), where once again the $FADH_2$ involved in this shuttle is replaced by $NADH_m$. The malate–aspartate shuttle is not taken into account.

Finally, oxidative phosphorylation is summarized in reaction 16. Reaction 15 ensures the consumption of ATP produced by glycolysis and oxidative phosphorylation.

The irreversible reaction 17 summarizes other dehydrogenases producing $NADH_m$. The orientation of this reaction is changed in comparison to the original Fig. 1 of the paper. We indicate the direction from NAD_m to $NADH_m$ in accordance with the v_{17} rate equation ($v_{17} = \beta_{17} n_1$). This is also in accordance with the differential equation (Eq. (11) of the Dynnik paper) expressing the variation of n_2 ($NADH_m$) where v_{17} has the same "+" sign as v_{11}, which expresses $NADH_m$ production.

The only regulation introduced in this model is the allosteric regulation of reaction v_1 (in reality phosphofructokinase) by AMP.

At steady state, the flux through reaction 1 (v_1) represents the entry of glucose in the system. The flux through reaction 2 or 7 (v_2 or v_7) is the glycerol-3-P shuttle. The flux through reaction 5 (v_5) is the total glycolytic flux which splits in anaerobic glycolysis (v_6), and aerobic glycolysis or the Krebs cycle (v_8, v_9, v_{10} or v_{11} which are equal, see below). Finally, v_{16} represents the respiratory chain.

We reproduce below the equations on which the system is based.

3. Equations of the model

The variables and the time are scaled according to (Eqs. (2)–(8) and Eq. (10) in the original paper):

$$a_1 = \frac{\mathrm{AMP}}{A_0}, \quad a_2 = \frac{\mathrm{ADP}}{A_0}, \quad a_3 = \frac{\mathrm{ATP}}{A_0},$$