13 Molecular mechanism responsible for the increase in 2,3-DPG concentration in human erythrocytes at high altitudes

A.G. Plotnikov, F.I. Ataullakhanov and V.M. Vitvitsky
Research Center for Hematology, Russian Academy of Medical Sciences Novozykovsky pr.4a, 125167 Moscow, Russia

Introduction

Since the 1960s, the 2,3-DPG concentration in human erythrocytes is considered to be a significant index of adaptation to hypoxia, because it increases at high altitudes [1–4]. White *et al.* [1] have found a 20% increase in the 2,3-DPG concentration at an altitude of 15 000 feet. The mechanism responsible for elevated 2,3-DPG at high altitudes is an as yet "unresolved problem of respiratory physiology" [2].

We proposed a mathematical model to describe this mechanism. Analysis of the model shows that the amount of 2,3-DPG associated with hemoglobin increases but free 2,3-DPG remains at an approximately constant level with increasing the altitude.

Mathematical model

We constructed the model by combining the model of glycolysis [5] and the model of Di Cera *et al.* describing hemoglobin interaction with organic phosphate and oxygen [6,7].

The limited space does not allow us to present this model comprehensively. Therefore, we describe here only its part concerning 2,3-DPG metabolism and organic phosphate interaction with hemoglobin and oxygen. The description of glycolysis and energy metabolism was given at the 8th International meeting on the BioThermoKinetics in Göteborg [5].

2,3-DPG in the human erythrocyte exists in two forms: free and hemoglobin-bound. Although the relationship between these two forms changes during the oxygenation-deoxygenation cycle, we do not consider these changes in the model.

The model variables are the average concentrations of free 2,3-DPG ([23DPG]), 2,3-DPG bound to hemoglobin ([23DPGasHb]), and total 2,3-DPG ([23DPGsum]). They are related by the following equation (eq. 13.1):

$$[23DPGsum] = [23DPG] + [23DPGasHb] \tag{13.1}$$

The equations describing hemoglobin interaction with organic phosphate and oxygen (eqs. 13.2–13.6) are from [6, 7]:

$$[Hbsum] = [Hb_1] + [Hb_2] \tag{13.2}$$

Here, [Hbsum] denotes the total hemoglobin in human erythrocytes; $[Hb_1]$ is the hemoglobin free of 2,3-DPG, and $[Hb_2]$ is the hemoglobin bound to 2,3-DPG.

$$[Hb_1] = [Hb] \cdot P_0 \tag{13.3}$$

$$[Hb_2] = [Hb] \cdot P1 \cdot [23DPG] \tag{13.4}$$

Here, [Hb] denoted the concentration of free hemoglobin, and P_0 and P_1 are the polynomials (see [6] for their description):

$$P_0 = (1 + Kr \cdot q)^4 + L(1 + 2Kt \cdot q + \delta \cdot (Kt \cdot q)^2) \tag{13.5}$$

$$P_1 = \lambda_1(1 + Kr \cdot q)^4 + L(\lambda_2 + 2\lambda_3 Kt \cdot q + \delta \cdot \lambda_4 \cdot (Kt \cdot q)^2) \tag{13.6}$$

Here, q is the blood oxygen concentration (averaged over the entire blood volume), $Kr = 12$ Torr^{-1}, $Kt = 0.1$ Torr^{-1}, $L = 8 \times 10^7$, $\delta = 1.1$, $\lambda_1 = 370$ M^{-1}, $\lambda_2 = 3{\times}10^4$ M^{-1}, $\lambda_3 = 9 \times 10^3$ M^{-1}, and $\lambda_4 = 3.5 \times 10^3$ M^{-1}.

Hemoglobin binds 2,3-DPG at a 1:1 ratio [1], hence

$$[23DPGasHb] = [Hb_2] \tag{13.7}$$

Substituting this into eqs. 13.2 to 13.4 and 13.7, we arrive at:

$$[23DPGasHb] = [Hbsum]/(1 + P_0/(P_1 \cdot [23DPG])) \tag{13.8}$$

The concentration of hemoglobin-bound 2,3-DPG may be derived from eq. 13.8. It depends on the oxygen concentration and the concentration of free 2,3-DPG.

The enzymes of the 2,3-DPG bypass, diphosphoglycerate mutase and diphosphoglycerate phosphatase, determine the total 2,3-DPG concentration in human erythrocytes. Both enzymatic activities depend on the free 2,3-DPG concentration [5]:

$$\frac{d}{dt}[23DPG] = v_{DPGM} - v_{DPGP} \tag{13.9}$$

Here, v_{DPGM} and v_{DPGP} are the rates of diphosphoglycerate mutase and diphosphoglycerate phosphatase.

Diphosphoglycerate-mutase and diphosphoglycerate-phosphatase reactions are described by eqs. 13.10 and 13.11:

$$v_{\mathrm{DPGM}} = W_{DPGM}\frac{[13\mathrm{DPG}]}{K_{111} + K_{112}[13\mathrm{DPG}] + K_{113}[23\mathrm{DPG}]} \tag{13.10}$$

$$v_{\mathrm{DPGP}} = W_{\mathrm{DPGP}}\frac{[23\mathrm{DPG}]}{[23\mathrm{DPG}] + K_{121}(1 + ([2\mathrm{PG}] + [3\mathrm{PG}])/K_{122})} \tag{13.11}$$

Here, W_{DPGM} = 4300 mM/h, K_{111} = 0.04 mM, K_{112} = 0.013, K_{113} = 2, W_{DPGP} = 0.52 mM/h, K_{121} = 0.02 mM, K_{122} = 0.006 mM; [13DPG], [3PG], and [2PG] are the concentrations of 1,3-diphosphoglycerate, 3-phosphoglycerate, and 2-phosphoglycerate (variables of the model as described in [5]).

Results and discussion

Hemoglobin in human erythrocytes is present in two forms, T and R. The affinity of T hemoglobin for oxygen is low, and that of the R form is high. With decreasing q, T hemoglobin concentration rises and that of R hemoglobin drops.

As the affinities for 2,3-DPG of T and R hemoglobins are high and low, respectively, a decrease in q causes T hemoglobin and hemoglobin-bound 2,3-DPG concentrations to rise.

In the model, the steady-state concentration of free 2,3-DPG does not change with decreasing q. As q decreases, the free 2,3-DPG concentration first falls and then returns to its initial value. (This fall is accounted for by the increase in the T hemoglobin concentration). With decreasing free 2,3-DPG concentration, v_{DPGM} surpasses v_{DPGP} and causes the total 2,3-DPG concentration to rise and the free 2,3-DPG concentration to return to the initial level.

Fig. 13.1 demonstrates the dependence of the total and hemoglobin-bound 2,3-DPG concentrations on the blood oxygen concentration q. Note that the relationship between the partial oxygen pressure in the atmosphere and average oxygen concentration in the blood exhibits inter-individual variation. Correspondingly, at the same partial oxygen pressure in the atmosphere, 2,3-DPG varies greatly in different individuals.

The normal oxygen concentration in arteries q_{art} is equal to 93 Torr at the sea level [8]. Therefore, for the mixed blood, we assumed q to be about 70 Torr. According to the model, in the steady-state, [23DPG] = 2.5 mM, [23DPGasHb] = 2.53 mM, and [23DPGsum] = 5.03 mM.

At the altitude of 4.5 km, oxygen pressure in atmosphere decreases from 160 to 90 Torr. Therefore, the oxygen concentration in arteries would decrease from 93 to 47 Torr [8]. Using the model, we estimated [23DPGsum] at 5.91 mM,

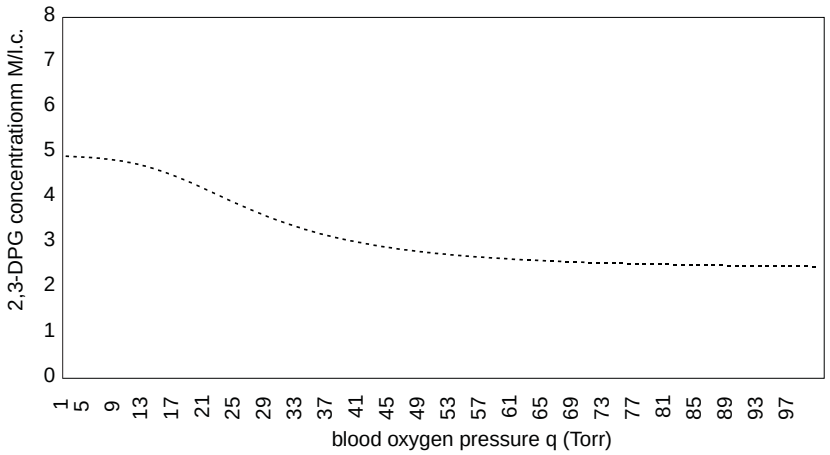

Fig. 13.1 Total 2,3-DPG (solid line) and hemoglobin-bound 2,3-DPG (dotted line) plotted versus q (blood oxygen concentration)

[23DPG] mM at 2.5 mM, and [23DPGasHb] at 3.41 mM for q = 30 Torr, corresponding to the altitude of 4.5 km.

Total 2,3-DPG continues to increase during 2 days after climbing in both experiments and the model. The model predicts an 18% increase in the total 2,3-DPG. The experimentally observed value was 20% [1].

Using the model, we assessed the contribution of 2,3 DPG to the adaptation of the organism to hypoxia. At a height of 5 km, q_{art} = 47 Torr and q_{vein} = 25 Torr. We calculated the amount of blood-transported oxygen for two cases: (i) [23DPGsum] = 5.03mM; (ii) [23DPGsum] = 5.91mM.

According to the model, the rise in the 2,3 DPG concentration from 5.03 to 5.91 increases the oxygen transport by 7%. Obviously, elevated 2,3-DPG can improve oxygen transport in hypoxia.

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