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REVIEW ARTICLE

THE MOLECULAR MECHANISM OF THE MEMBRANE REDOXY POTENTIAL: A THREE-STATE-DEPENDENCY CLOSED 9-STEP STEPPED CYCLE OF PROTON CONDUCTANCE

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ABSTRACT

The new variant of equation of metabolism as " Donators (first stage of proton conductance) + membrane - redox potentials three state line system + O_2 (Hemoglobin of pulmonary capillary -8-th stage, Hemoglobin of tissue-87 trillion cell surrounded capillary-9-th stage) + ADP + Pi + (H^+ + $nH^+_{memb.space}$ – proton gradient-4-th stage) = (ATP + heat energy-5 -th stage) + H_2O (5-th stage) + (nH^+_{matrix}) + CO_2(second stage of proton conductance), "which give to us the possility to speak about of existing of two forms of free protons as at first: left side of equation - H+ membrane space – formed by this reaction as - CHO- food molecules, separated from CHO - H- hydrogen atom , separated from hydrogen atom free proton, free electron - proton gradient – at second : right side of equation H+ matrix is the main Molecular mechanism of the Membrane Redoxy Potential: A Three-State-Dependency Closed 9-Step Stepped Cycle of Proton Conductance. In such way all processes including from Sixth stage - to Ningh stage of proton conductance may be describe as carbon dioxide diffuses in to the plasma and red blood cells (in the tissue capillaries), carbon dioxide is released from red blood cells, proton is released from red blood cells (in the pulmonary capillaries), oxygen diffuses in to plasma from alveolus, oxygen binds to hemoglobin, in the chloride shift as HCO_3 diffuses in to red blood cells, proton and carbon dioxide are combined with hemoglobin, that has released oxygen, promotes the release of oxygen from hemoglobin – oxygen diffuses out of red blood cells and plasma in to tissues – mitochondria of 87 trillion cells through oxygen channeling lipid based pathways.

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INTRODUCTION

The new variant of equation of metabolism as "Donators (first stage of proton conductance) + membrane - redox potentials three state line system + O_2 (Hemoglobin of pulmonary capillary -8-th stage, Hemoglobin of tissue-87 trillion cell surrounded capillary-9-th stage,) + ADP + Pi + (H^+ + $nH^+_{memb.space}$ – proton gradient-4-th stage) = (ATP + heat energy-5 -th stage) + H_2O (5-th stage) + (nH^+_{matrix}) + CO_2(second stage of proton conductance)", which give to us the possility to speak about of existing of two forms of free protons as at first: left side of equation - H^+ membrane space - formed by this reaction as - CHO- food molecules, separated from CHO - H- hydrogen atom, separated from hydrogen atom free proton, free electron - proton gradient - at second: right side of equation H^+_{matrix} is the main Molecular mechanism of the Membrane Redoxy Potential: A Three-State-Dependency Closed 9-Step Stepped Cycle of Proton Conductance. The discovery of the closed 9-step cycle by us has biological and medical significance, as did the DNA molecular structure revealed by Watson and Krick because the 9-stage cycle of proton conductance resembled a big electric station, which provided all 87 trillion cells, including brain cells and myocardial cells, with ATP, NADPH, and ATP-based genetic materials such as DNA, RNA, heat energy, CO_2, oxygen, free protons, and electrons (16). The membrane - based mechanism for making ATP were formed very early in life history (Park 2009), its essential features retained in the long evolutionary journey from the time of the early procaryotes to modern cells during last 3,6 billion years converted to membrane - redox potential three state (alpha state with high oxidation potential, beta state with high reduction potential, gamma state with low redox potential) line system as very important member of reaction "Donators (first stage of proton conductance) + membrane - redox potentials three state line system + O_2 (Hemoglobin of pulmonary capillary -8-th stage, Hemoglobin of tissue-87 trillion cell surrounded capillary-9-th stage,) + ADP + Pi + (H^+ + $nH^+_{memb.space}$- proton gradient-4-th stage) = (ATP + heat energy-5 -th stage) + H_2O (5-th stage) + (nH^+_{matrix}) + CO_2(second stage of proton conductance (1,5,8). According to the suggestion of Professor M. Ambaga (2016), the membrane-based mechanism for making ATP consists of the full nine-step cycle of proton and electron conductance inside the human body. As electrons and protons derived from the oxidation of food substrates are transferred along electron carriers, protons (H^+) flow back down its electrochemical gradient through ATP synthase, which catalyzes the energy

requiring the synthesis of ATP from ADP and inorganic phosphate (Alberts B, et al.) as follows:H atoms contained in food molecules through the 1-th stage of the full 9-step cycle of electron and proton conductance as release of proton, electrons together from food substrates under the undirect action of oxygen released from the membrane surroundings of erythrocytes converted to NADH and $FADH_2$ (2,3, 15, 9,6,5). After these stages as conversion of H atoms contained in food molecules to NADH, $FADH_2$ have been started the next stages of conductance of free protons, including the 5-th stage of the full 9 stepped cycle of electron and proton conductance as translocation of proton to inter membrane space of mitochondria without accompanying electron, the 6-th stage as creation of proton gradient in the inter membrane space of mitochondria and following transfer of proton to matrix through ATP synthase, the 7-th stage as formation of metabolic water in the mitochondrian matrix by protonation of activated oxygen after obtaining electrons by matrix proton, the 8-th stage as diffusion of proton from mitochondrial matrix of all cells and metabolic water formed during protonation of molecular oxygen by matrix proton entered through plasma membrane of red blood cells by HCO_3/ CL - shift mechanism, also the 9-th stage as metabolic water entered to red blood cells reacts with CO_2 formed in the 2-stage by formation H_2CO_3, which is followed by reaction as $H_2CO_3 = H + HCO_3$ and released during this stage free proton promotes the release of oxygen from hemaglobin, i.e. occur the meeting of CO_2 formed in the 2-stage with metabolic water formed in the 7-th stage of the full 9 stepped cycle of electron and proton conductance inside red blood cells (1,16, 6,7,8).

RESULTS

Proposed by us the full nine-step cycle of electron and proton conductance inside the human body demonstrated that:

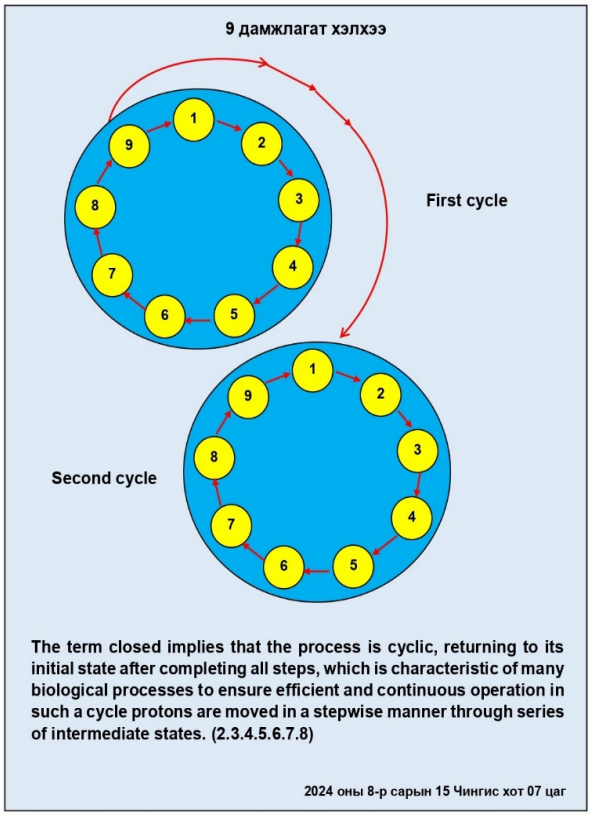
First stage of proton conductance: oxygenchanneling to mitochondria of 87 trillion cells; oxygen channeling: oxygen has been assumed to diffuse across cell bodies; very low oxygen solubility in the cytosol, reported High-solubility ‘channels’ likely formed by the endoplasmic reticulum by haem-bearing cytochrome P450 molecules; accelerated oxygen diffusion via lipid droplets; lateral diffusion within mitochondrial membranes; mitochondria;release of hydrogen atoms, protons, and electrons from food molecules; Krebs cycle under the influence of the ninth stage as release of oxygen from hemoglobin.

The second stage of proton conductance is carbon dioxide, generated by the Krebs cycle in the mitochondria of 87 trillion cells.

Third stage: The processes conducted with connection to the formation of NADH, FADH, Coenzyme Q, and Cytochrome C oxidase.

Fourth stage: The processes conducted with the formation of a proton gradient from protons and the connection of oxygen with electrons.

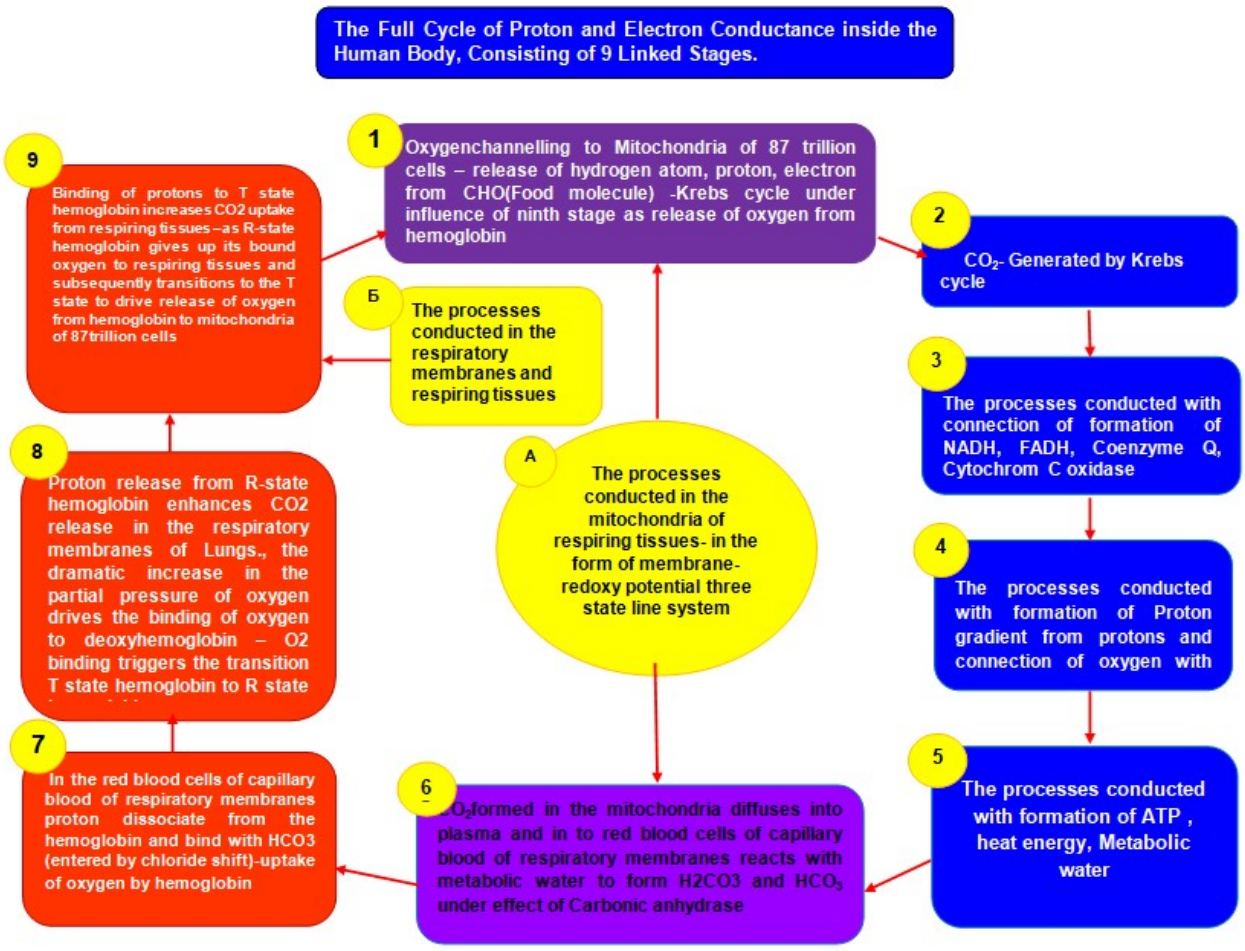
Fifth stage: The processes conducted with the formation of ATP, heat energy, and metabolic water.



In the sixth stage, PO_2 formed in the mitochondria diffuses into plasma and into red blood cells. The capillary blood of respiratory membranes reacts with metabolic water to form H_2CO_3 and HCO_3. From the mitochondria, carbon dioxide diffuses into the plasma and into red blood cells.

Seventh stage: In the red blood cells of the capillary blood of the respiratory membranes, protons dissociate from hemoglobin and bind with HCO_3 (entered by chloride shift) - uptake of oxygen by hemoglobin. In the red blood cells of capillary blood, CL shift occurred between mitochondria, plasma, and hemoglobin. Eigth stage of proton conductance: proton release from R-state hemoglobin enhances CO_2 release in the respiratory membranes of the lungs; the dramatic increase in the partial pressure of oxygen drives the binding of oxygen to deoxyhemoglobin; O_2 binding triggers the transition of T-state hemoglobin to R-state hemoglobin. Oxygen diffuses into the plasma and into red blood cells from the alveolus. Oxygen binds to hemoglobin; in the chloride shift, as HCO_3 diffuses into red blood cells, bicarbonate ions and protons combine to replace H_2CO_3, carbon dioxide is released from hemoglobin, and hydrogen ions are released from hemoglobin.

Ningh stage of proton conductance: binding of protons to T-state hemoglobin increases CO_2 uptake from respiring tissues. As R-state hemoglobin gives up its bound oxygen to respiring tissues and subsequently transitions to the T-state, it s to drive release of oxygen from hemoglobin to the mitochondria of 87 trillion cells. Carbon dioxide and hydrogen ions combine with hemoglobin, which has released oxygen, to promote the release of oxygen from hemoglobin. Oxygen is released from hemoglobin, which diffuses out of red blood cells and plasma into tissues (the mitochondria). In such way all processes including from Sixth stage - to Ningh stage of proton conductance may be describe as carbon dioxide diffuses in to the plasma and red blood cells (in the tissue capillaries), carbon dioxide is released from red blood cells, proton is



released from red blood cells (in the pulmonary capillaries), oxygen diffuses in to plasma from alveolus, oxygen binds to hemoglobin, in the chloride shift as HCO_3 diffuses in to red blood cells, proton and carbon dioxide are combined with hemoglobin, that has released oxygen, promotes the release of oxygen from hemoglobin - oxygen diffuses out of red blood cells and plasma in to tissues - mitochondria of 87 trillion cells through oxygen channeling lipid based pathways.

DISCUSSION

Until now, it has not appeared the appropriate variant of System models of Human body which gives the possibility to better understand theunrevealed some regulations of Human body, including the membrane redoxy potential, the three state-dependent, nine-step full cycle of proton conductance, the four compartments, and the 10 functional systems (2,3,16). In this connection, by us has been proposed the new idea about of Proton dependent System models of Human body by revealing a close relationship between the following two expressions: life has become dependent on the presence of protons and electrons, which were formed during the events called the Big Bang 15 years ago, and the presence of protons from peripheral tissues favors the formation of a salt bridge in the histidine residue of betta subunits (Harpers Biochemistry). According to the full 9 stepped cycle of proton conductance proposed by professor M. Ambaga (2016) - 7-th stage conducted as formation of metabolic water in the mitochondrian matrix by protonation of activated oxygen after obtaining electrons by matrix proton, the 8-th stage conducted as diffusion of proton from mitochondrial matrix of all cells and metabolic water formed during protonation of molecular oxygen by matrix proton entered through plasma membrane of red blood cells by HCO3/ CL –shift mechanism, the 9-th stage is distinguished by this as metabolic water entered to red blood cells reacts with CO_2 formed in the 2-stage by formation H_2CO_3, which is followed by reaction as $H_2CO_3 = H + HCO_3$ and released during this stage free proton promotes the release of oxygen from hemaglobin, i.e. occurred the combination of CO_2 formed in the 2-stage with metabolic water formed in the 7-th stage of the full 9 stepped cycle of electron and proton conductance inside red blood cells. But now we have some elucidation in relation to the eighth stage of proton conductance: proton release from R-state hemoglobin enhances CO_2 release in the respiratory membranes. The increase in the partial pressure of oxygen drives the binding of oxygen to deoxyhemoglobin. O_2 binding is accompanied by the transition of T-state hemoglobin to R-state hemoglobin. The protons combine with bicarbonate to increase the concentration of carbonic acid, which in turn favors the carbonic anhydrase-catalyzed dehydration of H_2CO_3 to form CO_2, which can then be disposed of by exhalation-mediated coupling of the transition of hemoglobin between T and R states (Kennelly P, Botham K, McGuinness). Carbon dioxide generated in peripheral tissues combines with water to form carbonic acid, which dissociates into protons and bicarbonate ions. Deoxyhemoglobin acts as a buffer by binding protons and delivering them to the lungs. In the lungs, the uptake of oxygen by hemoglobin releases protons that combine with the bicarbonate ion to form carbonic acid, which, when dehydrated by carbonic unhydrase, becomes carbon dioxide, which is then enhaled (Kennelly P, Botham K, McGuinness). Ningh stage of proton conductance: binding of protons to T-state hemoglobin increases CO_2 uptake from respiring tissues. As R-state hemoglobin forms in this stage, it gives up its bound oxygen to the mitochondria of 87 trillion cells and subsequently

transitions to the T-state. The absorbtion of protons both buffers the pH of the acidifying red blood cells. The greater availability of H+ in this stage of proton conductance favors the formation of the T state by enhancing the release of oxygen. Proton binding by T-state hemoglobin enables the high levels of CO_2 in respiring tissues consisting of 87 trillion cells to release oxygen from hemoglobin to 87 trillion cells, resulting in a decrease in the pH of red blood cells in venous blood. All these processes conducted in the full 9-step cycle of proton conductance inside the human body are regulated by the membrane-redox potentials three-state line system of" Donators (first stage of proton conductance) + membrane - redox potentials three state line system + O_2 (Hemoglobin of pulmonary capillary -8-th stage, Hemoglobin of tissue-87 trillion cell surroundedcapillary-9-th stage,) + ADP + Pi + (H^+ + $nH^+_{memb.space}$- proton gradient-4-th stage) = (ATP + heat energy-5 -th stage) + H_2O (5-th stage) + (nH^+_{matrix}) + CO_2(second stage of proton conductance reaction medium located in 87 trillion cells of the human body. Factors conditioning the release of electrons and protons from food substrates, the release of oxygen from hemoglobin, and the release of carbon dioxide from the body are identified.

We also understand the stage that initiates and concludes the cycle of electron and proton conductance inside the human body. According to the full 9-step cycle of electron and proton conductance proposed by us, certain studies have revealed the transition of R-T and T-R states of hemoglobin, offering the possibility to elucidate the eighth and ninth stages of the closed 9-staged cycle of proton conductance (Kennelly P, Botham K, McGuinness). Without a full nine-step cycle of electron and proton conductance inside the human body, it is absolutely impossible to maintain any form of life process. Ningh stage of proton conductance: binding of protons to T-state hemoglobin increases CO_2 uptake from respiring tissues. As R-state hemoglobin gives up its bound oxygen to respiring tissues and subsequently transitions to the T-state, it drives the release of oxygen from hemoglobin to the mitochondria of 87 trillion cells.

Carbon dioxide and hydrogen ions combine with hemoglobin, which has released oxygen, to promote the release of oxygen from hemoglobin. Oxygen is released from hemoglobin, which diffuses out of red blood cells and plasma into tissues (the mitochondria). In such way all processes including from Sixth stage - to Ningh stage of proton conductance may be describe as carbon dioxide diffuses in to the plasma and red blood cells (in the tissue capillaries), carbon dioxide is released from red blood cells, proton is released from red blood cells (in the pulmonary capillaries), oxygen diffuses in to plasma from alveolus, oxygen binds to hemoglobin, in the chloride shift as HCO_3 diffuses in to red blood cells, proton and carbon dioxide are combined with hemoglobin, that has released oxygen, promotes the release of oxygen from hemoglobin - oxygen diffuses out of red blood cells and plasma in to tissues - mitochondria of 87 trillion cells through oxygen channeling lipid based pathways.

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