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THE FULL 9 STEPPED CYCLE OF PROTON, ELECTRON CONDUCTANCE AND NORMAL EXISTENCE OF HUMAN BODY

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ABSTRACT

In the Our first imagination about existence of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance as very important precondition of normal existence of human body was connected with these regularly repeated processes as the transfer of electron to KoQ with the transfer of protons across a membrane to intermembrane space with participation of complex I-NADH: ubiquinone oxidoreductase, during which two electrons are removed from NADH and ultimately transferred to ubiquinone (UQ) - complex I also translocates four protons (H^+) across the membrane and also under influence of complex III - cytochrome bc_1 complex or $CoQH_2$ - cytochrome c reductase two electrons are removed from QH_2 at the Q_O site and total four protons are translocated. Also, our imagination about existence of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance was connected with these regularly repeated bioevents as that the cell respiration evolving early in the history of life was needed the involvement of the bioenergetical membrane structures and when pH of blood falls the affinity of hemoglobin to O_2 decreased, which accompanied by release of O_2 in tissues, and increased CO_2 in blood led to elevation of H^+ production, and when H^+ binds to deoxyhemoglobin, which accompanied by decrease of accesibility of O_2 to hemoglobin and in this case release O_2 is increased. The membrane - based mechanism for making ATP as one of very important parts of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance, within which electrons and protons released from food substrates are transferred along a electron carriers, protons (H+) flows back down its electrochemical gradient through ATP synthase, which catalyses the energy requiring synthesis ATP from ADP and inorganic phosphate. About 2×10^9 years ago, the O_2 released owing to photosynthesis in cyanobacteria began to accumulate in the atmosphere. Once both organic molecules as food substrates and O_2 as electron acceptor had become abundant, electron - transport chains became adapted for the transport of electrons from NADH to O_2, and efficient aerobic metabolism developed in many bacteria with following development of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance in the level of whole organism with involvement of hemaglobins of vertebrate erythrocytes, which perform two major biological functions transport of O_2 from respiratory organ to peripheral tissues, and transport of CO_2 and protons from peripheral tissues to respiratory organ for subsequent excretion within last 8 and 9 stages of closed proton cycle, proposed by us. The new conception relating to existence of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance have been included these processes as electron transfer with the transfer of protons (H^+ ions) across a membrane with using of three proton pumps - heart of the electron transport process as I, III, and IV complexes within first 1-7 stages of closed proton cycle, proposed by us, resulting to trans membrane proton gradient, which is used to produce useful biological works by using ATP and reducing power (as NADPH).

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INTRODUCTION

The membrane - based mechanism for making ATP were formed very early in life history (Park MA) and its essential features retained in the long evolutionary journey from the time of the early procaryotes to modern cells during last 4, 5 billion years (15) by converting 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 (Ambaga and Tumen-Ulzii, 2016; Ambaga, 2016 & 2017). By us established that the basic components of membrane redoxy potential three state line systems, which is heart of 9 stepped closed cycle of proton conductance as follows:

a. Third stage of the membrane - redox potential, a three state line system dependent - full 9 stepped cycle of proton conductance is distinguished by transfer of electron to KoQ with the transfer of protons across a membrane to intermembrane space with participation of complex I-NADH: ubiquinone oxidoreductase, during which two electrons are removed from NADH and ultimately transferred to ubiquinone (UQ) - complex I also translocates four protons (H^+) across the membrane and also under influence of complex III - cytochrome bc_1 complex or $CoQH_2$ - cytochrome c reductase two electrons are removed from QH_2 at the Q_O site and total four protons are translocated.
b. Fourth stage of the membrane - redox potential, a three state line system dependent - full 9 stepped cycle of proton conductance is distinguished by transfer of electron to cytochrom C and oxygen with the transfer of protons across a membrane to intermembrane space with participation of Complex IV-cytochrome c oxidase, during which four electrons are removed from four molecules of cytochrome c and transferred to molecular oxygen (O_2), producing two molecules of water, and eight protons are removed from the mitochondrial matrix, only four are translocated across the membrane.
c. Fifth stage of the membrane - redox potential, a three state line system dependent - full 9 stepped cycle of proton conductance is distinguished by the formation of metabolic water in the mitochondrian matrix by oxidation of proton by molecular oxygens i.e, by protonation of molecular oxygen by matrix proton with participation of cytochrome C oxidase within complex IV, during which four electrons are removed from four molecules of cytochrome c and transferred to molecular oxygen (O_2), producing two molecules of water, and eight protons are removed from the mitochondrial matrix, only four are translocated across the membrane
d. The seventh stage of the membrane - redox potential, a three state line system dependent - full 9 stepped cycle of proton conductance is characterized by processes occurred in the *Complex V* of the electron transport chain. The F_O component of ATP synthase acts as an ion channel that provides for a proton flux back into the mitochondrial matrix. It is composed of a, b and c subunits. Protons in the inter-membranous space of mitochondria first enters the ATP synthase complex through *a* subunit channel. Then protons move to the c subunits. In humans, there are 8 c subunits, thus 8 protons are required.
e. Ninth stage of the membrane - redox potential, a three state line system dependent - full 9 stepped cycle of proton conductance is characterized by processes as proton combine with hemoglobin(generation of HbH) which promotes the release of oxygen from hemoglobin, oxygen diffusion to all cells conditioning the release of proton, electron from food substratesin the 1-stage also proton released from hemoglobin promotes uptake of oxygen by hemoglobin, CO_2 promotes the generation of free proton by mecchanism as H_2CO_3.H+HCO_3, arbonic anhydrase catalyzes the formation of CO_2 from H_2CO_3 and CO_2 diffuse out in the alveoli (Ambaga and Tumen-Ulzii, 2015; Ambaga, 2016; Murray).

RESULTS AND DISCUSSION

It was interesting to give the answer to the principally important questions relating to as how protons made closed repeated movement by circulating through closed circle, accompanied by these processes as electron transfer with the transfer of protons (H^+ ions) across a membrane, through three proton pumps - the heart of the electron transport process, as I, III, and IV complexes, resulting to trans membrane proton gradient, which is used to produce useful work. Our first imagination about existence of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance as very important precondition of normal existence of human body was connected with these regularly repeated processes as the transfer of electron to KoQ with the transfer of protons across a membrane to intermembrane space with participation of complex I-NADH: ubiquinone oxidoreductase, during which two electrons are removed from NADH and ultimately transferred to ubiquinone (UQ) - complex I also translocates four protons (H^+) across the membrane and also under influence of complex III - cytochrome bc_1 complex or $CoQH_2$-cytochrome c reductase two electrons are removed from QH_2 at the Q_O site and total four protons are translocated. Also, our imagination about existence of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance was connected with these regularly repeated bioevents as that the cell respiration evolving early in the history of life was needed the involvement of the bioenergetical membrane structures and when pH of blood falls the affinity of hemoglobin to O_2 decreased, which accompanied by release of O_2 in tissues, and increased CO_2 in blood led to elevation of H^+ production, and when H^+ binds to deoxyhemoglobin, which accompanied by decrease of accesibility of O_2 to hemoglobin and in this case release O_2 is increased (Murray *et al.*). At first it was very difficult for us to describe that how occured the conductance of proton by closed cycle, starting from first stage of conductance and ending by repackaging of protons inside membrane surroundings of erythrocyte. Before developing the new conception, relating to existence of the membrane - based mechanism for making ATP consists of the full 9 stepped cycle of proton, electron conductance inside human body we did not know several facts as follows as :

- We did not know which stage of the full 9 stepped cycle of electron, proton conductance inside human body followed after Krebs cycle.
- We did not know where eaten food and air, taken through inhalation (oxygen) in the cycle of electron and proton conductance would meet inside the human body.

- We had little knowledge relating to the stages and factors that will cause the release of electrons and protons from food substrates.
- We had little knowledge relating to the stages and factors that will cause the release of oxygen from the hemaglobin.
- We had little knowledge relating to the stages and factors that will cause the release of carbon - dioxide from body.
- We did not know the stage from which stage started the cycle of electron and proton conductance inside human body.
- We did not know the stage in which ended the cycle of electron and proton conductance inside human body.
- We did not know from how many stages have been consisted the full 9 stepped cycle of electron and proton conductance inside the human body (Ambaga, 2016).

In this connection, we, at first proposed that the full 9 stepped cycle of proton conductance inside human body, starts from the release of protons and electrons from food substrates (first stage) and ends by the final accumulation of free protons in the form of HbH inside the erythrocytes, allowing the promotion of oxygen intake by human body and the removal of carbon dioxide from the human body (last stages of closed cycle) (Figure 1). By our suggestion, the evolution history of development of life processes in our planet during last billion year should build the full closed cycle of protons, which have been included a these processes as electron transfer with the translocation of protons (H^+ ions) across a membrane with using of three proton pumps - heart of the electron transport process as I, III, and IV complexes, resulting to trans membrane proton gradient, which is used to produce useful biological works (Ambaga, 2017). What about the history of discovery of full closed cycle of electron, proton conductance, during our investigation we had been succeeded to find first stage of the full closed cycle of electron, proton conductance, which features may be described as release of proton, electron from food substrates under the undirect action of oxygen released from membrane surroundings of erythrocyte in the ninth stage, which we named as first stage of the full closed cycle. After this we had been succeeded to find the end 9-th stage of the full closed cycle of electron, proton conductance, which basic features may be described as proton combine with hemoglobin (generation of HbH) which promotes the release of oxygen from hemoglobin, oxygen diffusion to all cells conditioning the release of proton, electron from food substrates in the first stage also proton released from hemoglobin promotes uptake of oxygen by hemoglobin, CO_2 promotes the generation of free proton by mecchanism as H_2CO_3.H + HCO_3, carbonic anhydrase catalyzes the formation of CO_2 from H_2CO_3 and CO_2 diffuse out in the alveoli. In this connection it was became clear that the 8-th stage of the full closed cycle had been distinguished by the diffusion of three important factors as protons from mitochondrial matrix of all cells by sodium/proton antiporter mechanism, andalso in the form of HCO_3 and metabolic water through plasma membrane of red blood cells with participation of aquaporin protein channels, also entry of CO_2 formed in the second stage of closed cycle and entry of oxygen from lung. In such way, we had been succeeded to find the first three stages of the full closed cycle of electron, proton conductance, which features may be described as release of proton, electron from food substrates under the undirect action of oxygen released from membrane surroundings of erythrocyte in the 9-th stage and, the transfer of proton, electron to NADH, $FADH_2$ with release of CO_2 in Krebs cycle, and transfer of electron to KoQ with the transfer of protons across a membrane to intermembrane space. By our suggestion the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance have been divided in two parts as A part and B part as :

The specifics of A part of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance is distinguished by electron transport chain (ETC) is a series of complexes that transfer electrons from electron donors to electron acceptors via redox reactions, and couples this electron transfer with the transfer of protons (H^+ ions) across a membrane as at first :

Complex I-NADH: ubiquinone oxidoreductase, two electrons are removed from NADH and ultimately transferred to ubiquinone (UQ) - complex I also translocates four protons (H^+) across the membrane, thus producing a proton gradient-NADH is oxidized to NAD^+, by reducing Flavin mononucleotide to $FMNH_2$ in one two-electron step-$FMNH_2$ is then oxidized in two one - electron steps, each electron thus transfers from the $FMNH_2$ to an Fe-S cluster, from the Fe-S cluster to ubiquinone (Q) - during this process, four protons are translocated from the mitochondrial matrix to the intermembrane space, at second:

Complex II-succinate-CoQreductase, but unlike complex 1, no protons are transported to the intermembrane space, at third :

Complex III - cytochrome bc_1 complex or $CoQH_2$-cytochrome c reductase, two electrons are removed from QH_2 at the Q_O site and total four protons are translocated, at fourth :

Complex IV-cytochrome c oxidase, four electrons are removed from four molecules of cytochrome c and transferred to molecular oxygen (O_2), producing two molecules of water, and eight protons are removed from the mitochondrial matrix, only four are translocated across the membrane, at fifth :

Complex V of the electron transport chain. The F_O component of ATP synthase acts as an ion channel that provides for a proton flux back into the mitochondrial matrix. The efflux of protons from the mitochondrial matrix creates an electrochemical gradient (proton gradient).

This gradient is used by the F_OF_1ATP synthase complex to make ATP via oxidative phosphorylation. In such way, all biological events, which have been occurred within first 7 stages of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance are conditioned by equation as " Donators (glucose, aminoacids, fatty acids) + membrane redox potentials three-state line system + acceptor as $O_2 + ADP + Pi + H^+ + nH^+_{memb.space}$ = (ATP + heat energy) + H_2O + nH + matrix + CO_2"

In the framework of biological events as "the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance" would be conducted a following processes in first 7 stages as :

1. First stage-Release of proton,electron from food substrates under the undirect action of oxygen released from membrane surroundings of erythrocyte in the 9 stage

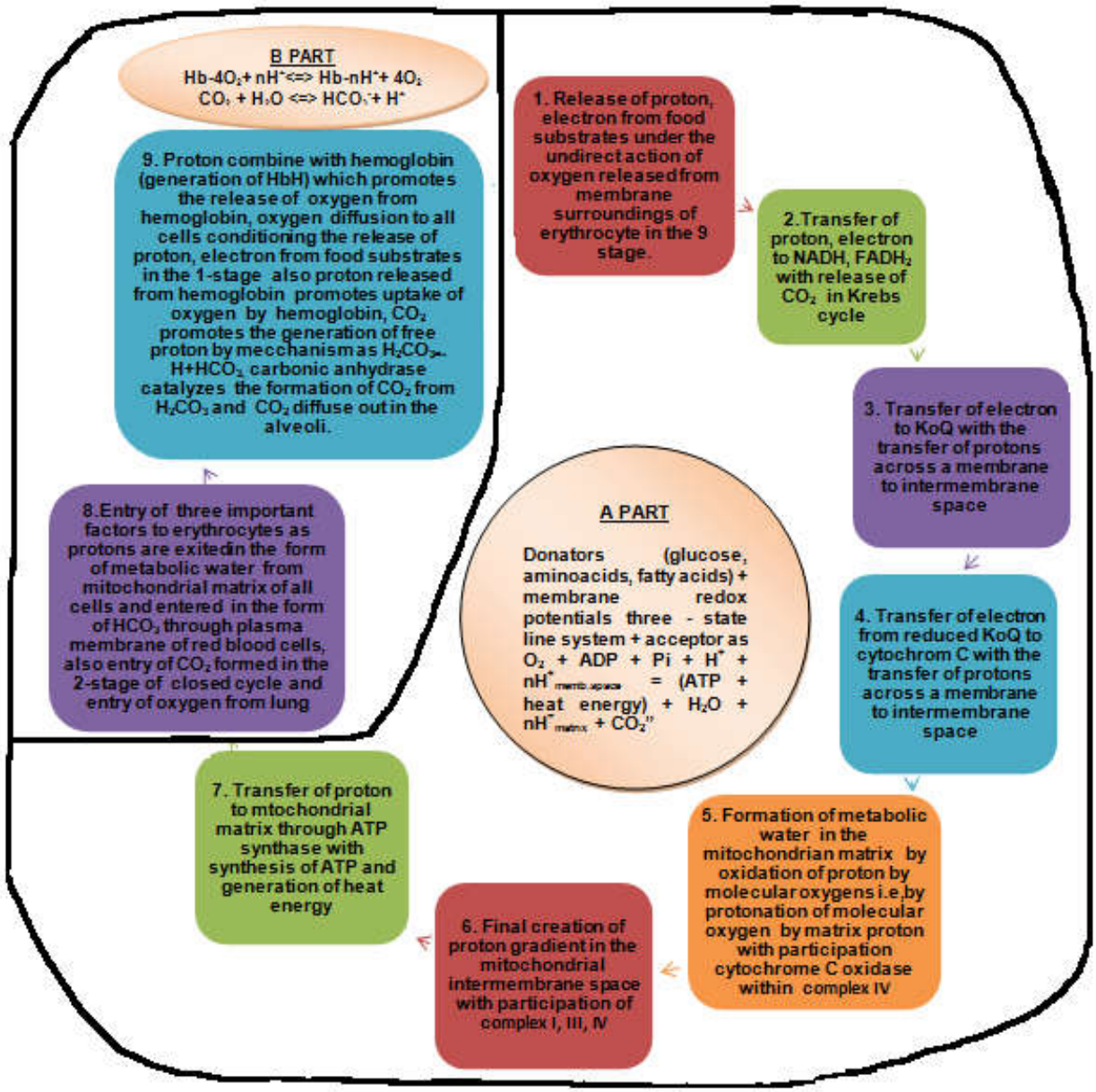

Figure 1. The final variant of closed cycle of proton conductance, consisting of A and B parts

2. Second stage-Transfer of proton, electron to NADH, $FADH_2$ with release of CO_2 in Krebs cycle
3. Third stage -Transfer of electron to KoQ with the transfer of protons across a membrane to intermembrane space with participation of complex I-NADH: ubiquinone oxidoreductase, during which two electrons are removed from NADH and ultimately transferred to ubiquinone (UQ) - complex I also translocates four protons (H^+) across the membrane and also under influence of complex III - cytochrome bc_1 complex or $CoQH_2$-cytochrome c reductase two electrons are removed from QH_2 at the Q_O site and total four protons are translocated.
4. Fourth stage -Transfer of electron to cytochrom C and oxygen with the transfer of protons across a membrane to intermembrane space with participation of Complex IV-cytochrome c oxidase, during which four electrons are removed from four molecules of cytochrome c and transferred to molecular oxygen (O_2), producing two molecules of water, and eight protons are removed from the mitochondrial matrix, only four are translocated across the membrane.
5. Fifth stage-Formation of metabolic water in the mitochondrian matrix by oxidation of proton by molecular oxygens i.e, by protonation of molecular oxygen by matrix proton with participation of cytochrome C oxidase within complex IV, during which four electrons are removed from four molecules of cytochrome c and transferred to molecular oxygen (O_2), producing two molecules of water, and eight protons are removed from the mitochondrial matrix, only four are translocated across the membrane
6. Sixth stage - Final creation of proton gradient in the mitochondrial intermembrane space with participation of complex I, III, IV
7. Seventh stage - Transfer of proton to mitochondrial matrix through ATP synthase with synthesis of ATP and generation of heat energy.

The specifics of B part of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance is distinguished by involvement of such reactions as Hb-$4O_2$+nH^+<=>Hb-nH^++ $4O_2$ and $CO_2 + H_2O <=> HCO_3^- + H^+$ in

last 8 stage and 9 stage of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance. In the framework of biological events as "the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance" would be conducted a following processes in last 8-th stage and 9-th stage as:

1. Eighth stage-Entry of three important factors to erythrocytes as protons are exited in the form of metabolic water from mitochondrial matrix of all cells and entered in the form of HCO_3 through plasma membrane of red blood cells, also entry of CO_2 formed in the 2-stage of closed cycle and entry of oxygen from lung
2. Ninth stage-Proton combine with hemoglobin (generation of HbH) which promotes the release of oxygen from hemoglobin, oxygen diffusion to all cells conditioning the release of proton, electron from food substratesin the 1-stage also proton released from hemoglobin promotes uptake of oxygen by hemoglobin, CO_2 promotes the generation of free proton by mecchanism as H_2CO_3.H+HCO_3, arbonic anhydrase catalyzes the formation of CO_2 from H_2CO_3 and CO_2 diffuse out in the alveoli.

In such way, the new conception relating to existence of the membrane redoxy potential three state dependent 9 stepped full cycle of proton conductance in two parts as A part and B part eventually describes the continuity of proton conductance inside human body, starting from food substrates, containing sum of electron, protons, ending by erythrocyte membrane surroundings containing last portions of protons, released from food under action of oxygens passing previous 9 stages.

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