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Perspective

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Putative Membrane Energy Reserves predicted by the Proton Capacitor Theory

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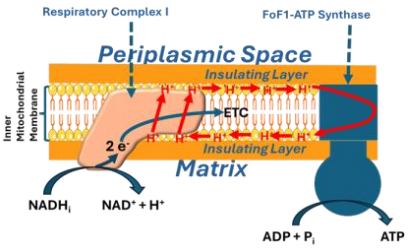
Summary



A significant number of reports indicate that oxidative phosphorylation (OXPHOS) occurs at multiple extra-mitochondrial sites, and this is not predicted by canonical mitochondrial criteria. This requires an update of the endosymbiotic theory by considering that ancestral bacteria, in becoming mitochondria, retained the ability to vesiculate and widespread distribution in organism districts of mitochondria derived vesicles (MDVs), which possess active OXPHOS, confirms that mitochondrial vesiculation is an active process in eukaryotic cells. MDVs can fuse with other membrane systems, and the succession of these processes appears to be a route for the export of OXPHOS to many subcellular and extra-cellular districts. Considering that the chemiosmotic theory is not applicable to extra-mitochondrial districts, a new theory is needed. Here is presented the Proton Capacitor Theory that is independent of the parameters Membrane Potential and Protomotive Force which has led to exhaustive discussions in the past and therefore the modalities with which the aerobic synthesis of ATP occurs both in the mitochondria and outside the mitochondria are greatly simplified by the Proton Capacitor Theory also with regards to computational thermodynamics. The proton movement scheme proposed here allows us to hypothesize that i) membranes can have a buffering action towards protons and therefore could be sites of rapidly usable energy deposits here called Proton Capacitors, and ii) it is possible that OXPHOS can occur in two phases, i.e. "charging" and "discharging" of the proton capacitor, consistently with the hypothesis that underlies the recently formulated Sleep Theory.

1. Introduction

After an oxygen-poor atmosphere the amount of oxygen raised enormously due to the oxygen production by photosynthetic bacteria during the Great Oxidation Event around 2.4–2.1 billion years ago [1]. So, to develop reactions that consumed oxygen, according to the endosymbiotic theory [2] , the aerobic bacteria were phagocytized by ancestral eukaryotes, but this statement needs to be updated because it is unlikely that bacteria, precursors of mitochondria, were engulfed by ancestral eukaryotes to supply the cell with ATP, a precious resource that would have helped these ancestral eukaryotes to even better phagocytose these "intruders". Some have rightly called it the "*Suicide Hypothesis*" [3].

It has been hypothesized [4] that bacteria, which possess oxidative phosphorylation (OXPHOS) but have poorly developed internal membranes (bacteria lack the cristae typical of mitochondria), in evolving into mitochondria received from ancestral eukaryotes [5] [6] the instructions for developing the surface of the internal membrane, i.e. the cristae, which in eukaryotes is highly developed in the form of endoplasmic reticulum. Thus a new hypothesis [4] prospects a true symbiosis, since bacteria transferred the OXPHOS machinery to the endoplasmic reticulum of ancestral eukaryotes, and ancestral eukaryotes transferred the instructions for highly developed internal membranes, i.e. the mitochondrial cristae, to bacteria which have become mitochondria.

This process which leads to the fusion of the mitochondrial membrane with other cellular membranes, endoplasmic reticulum first and foremost, means that the traditional OXPHOS mitochondrial functions -with coupled aerobic ATP synthesis- was expressed with high metabolite fluxes even in other cellular membranes and in fact it has been seen that OXPHOS is operative in vertebrate photoreceptors [7], myelin [8], platelets [9] plasma cells [10], sarcolemma of skeletal muscle [11] and everything suggests that extra-mitochondrial OXPHOS is operative in all subcellular districts of almost all living organisms.

This extra-mitochondrial diffusion of the OXPHOS which is considered to be exclusively mitochondrial requires the development of a new theory (here called “Proton Capacitor Theory”) on the coupling between proton movement and ATP synthesis. The “proton capacitor” is a system for the storage of ready-to-use energy which has already been applied to a hypothesis on the mechanisms of sleep [12].

In developing this new theory, we will take into account the principle that chemical processes are much more efficient if they occur in a homogeneous phase, and therefore the movement of protons is located exclusively within the proteolipid phase of the membrane.

2. Production of Mitochondrial Derived Vesicles

An property of bacteria must be taken into account, namely their extreme versatility in producing vesicles [13], property that has been retained by mitochondria that possess a plurality of molecular devices for vesicle production, namely Mitofusin 1 and 2, OPA1, Drp1 [14]. Interestingly, their functional deficit causes serious neurological pathologies [15]. The production of mitochondria-derived vesicles (MDVs) in eukaryotes is a highly active and multifaceted process that has been the subject of

much research in recent years 16[16] [16][17][18][19][20]. MDVs can fuse in the endoplasmic reticulum [21] where they form rafts that contain about 24% mitochondrial proteins [22]. The myelin sheath also contains rafts [23] [24] and this is consistent with the probable transfer of rafts to the oligodendrocyte endoplasmic reticulum (ER), which would then fuse with the forming myelin sheath.

The study of MDVs thus opens up fascinating scenarios, particularly the visionary idea that mitovesicles bud from mitochondria to spread and fuse with endocellular membrane, endoplasmic reticulum *in primis*, where ATP synthesis can occur *in situ* thanks to this import of the OXPHOS molecular machinery. Fig. 1 shows a possible vesiculation process of the mitochondrial inner membrane that passes through the maxi-pore Voltage Dependent Anion Channel (VDAC) [25] present on the mitochondrial outer membrane.

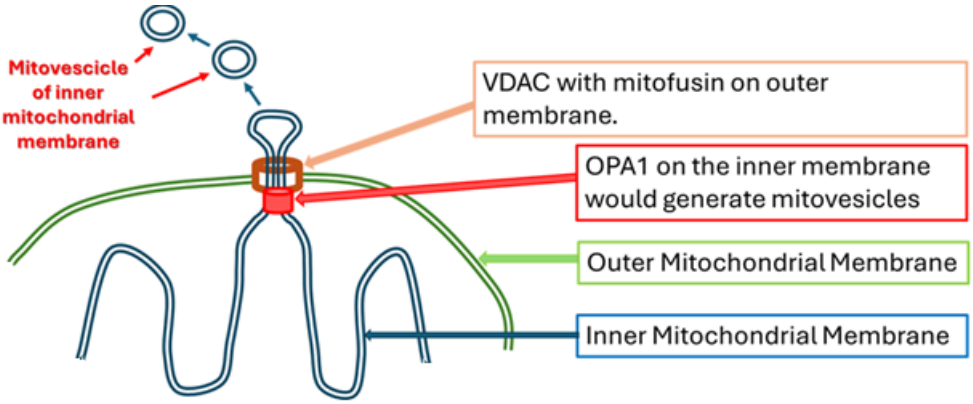


Figure 1. Proposal extrusion and delivery of mitovescicles of inner mitochondrial membrane fragments with "narrowing" by OPA1 inserted in inner mitochondrial membrane and extrusion through VDAC inserted in the outer mitochondrial membrane.

The VDAC, which is located in the outer membrane of the mitochondrion, plays an important role, as it may extrude the inner mitochondrial membrane to produce MDV. This hypothesis stems from the fact that VDAC is a protein with a structure of 19 antiparallel beta-barrel strands arranged in a barrel shape with an internal diameter of 3.15 nm [26] but it could tetramerize [27] forming new hydrogen bonds between one end of a VDAC with the end of another VDAC forming a ring with a diameter of ~13 nm, suitable for “squeezing” and extruding MDV.

This vesiculation process would exports the complex OXPHOS machinery to other sites, giving these sites the ability to synthesize ATP in situ.

All this goes beyond the traditional model that attributes the aerobic synthesis of ATP to mitochondria alone. Note that MDVs contain FoF1-ATP Synthase and synthesize ATP [28][29][30].

3. Formulation of Proton Capacitor Theory

Since the chemiosmotic theory [31] is not applicable to non-mitochondrial membranes expressing OXPHOS, it is necessary to formulate a new theory which I currently call Proton Capacitor Theory. In doing so, previous reports that have addressed this topic are taken into account [32] [33][34] [35][36] [19] [37] [38]. A recent article by S. Ji clearly identifies the limitations of the chemiosmotic theory [39]. Fig. 2A and 2B show, respectively, the scheme predicted by the chemiosmotic theory and the essential features of the theory formulated here. For simplicity, in the Fig. 2A-B only Respiratory Complex I is considered, which oxidizes NADH by initiating the Electron Transport Chain (ETC), coupled with the transfer of 4 H^+ for each molecule of NADH oxidized. On Fig. 2A (scheme of canonical chemiosmotic theory with coupling with FoF1-ATP synthase, protons are transferred to the intermembrane space by the action of Complex I; then the return of protons to the matrix, rotating the Fo Subunit of the FoF1-ATP Synthase nanomachine which synthesizes ATP in the matrix. This coupling called traditionally *delocalized coupling* cannot be accepted because no accumulation of protons is possible, otherwise the mitochondrion would collapse due to the high local acidity. Even Robert Williams, who was one of the most ardent opponents of the chemiosmotic theory, insisted that protons could not accumulate in the intermembrane space [40][41] . His famous objection is that protons transferred into intermembrane space would be lost in a “Pacific Ocean” [42]. In confirmation it has been highlighted that in the microvolume of a mitochondrion the protons can be very few [43].

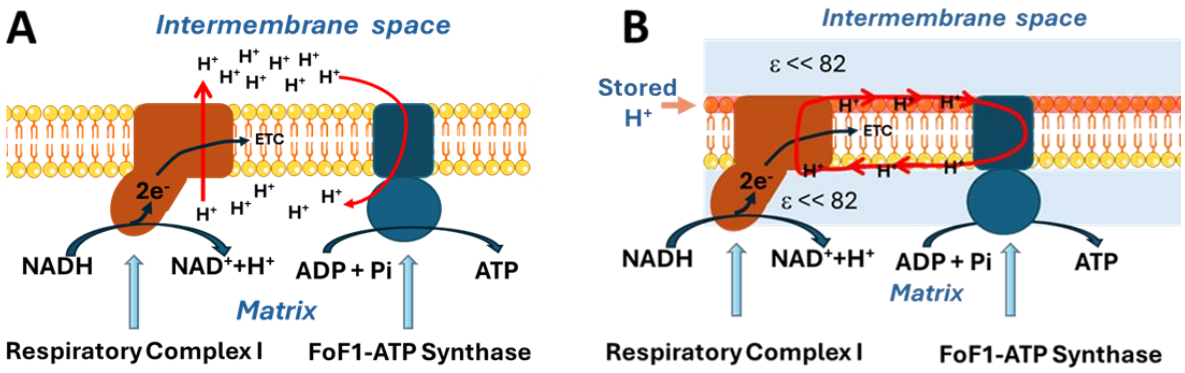


Figure 2. Only Respiratory complex I is considered, which oxidizes NADH by initiating the Electron Transport Chain (ETC), coupled with the transfer of 4 H+ for each molecule of NADH oxidized. In Fig. 2A the protons accumulated in the intermembrane space - which would generate the protomotive force – and return to the matrix, rotating the Fo subunit which transmits a molecular constriction to the F1 subunit with the consequent synthesis of ATP. This coupling called "delocalized coupling" should be rejected because no accumulation of free protons is possible, otherwise the mitochondrion would collapse due to the too low pH. In Fig. 2B, the existence on both sides of the membrane of a layer with dielectric constant $\varepsilon << 82$ is taken into account, confirming the insulation of the membrane with respect to the aqueous bulk. The protons moved by Respiratory Complex I migrate along phosphate and nitrogen

ionizable residues (such as ethanolamine and choline) of phospholipids in the intermembrane-facing hemilayer, pass through the Fo subunit of ATP synthase—with ATP synthesis by the F1 subunit—and return to ionizable residues of phospholipids in the matrix-facing hemilayer. But such groups can retain protons in the ionizable residues of phospholipids (highlight in orange) and this supports their function as proton capacitors. This scheme is consistent with "localized coupling".

In Fig. 2B (scheme of "Proton Capacitor Theory") the protons moving from Complex I travel along the ionizable head of the phospholipid facing the intermembrane space without being released into it, which is a well documented process [44][45][46][47]. The protons are captured by the Fo subunit of the FoF1-ATP synthase nanomachine, which synthesizes ATP, and can return to Respiratory Complex I by traveling along the ionizable "head", i.e. phosphate and basic group as etanolamine and choline, of the phospholipid facing the matrix. This groups can retain proton by accumulating them and this is the core of the Proton Capacitor Theory. It is important to take into account that the inner mitochondrial membrane is isolated from the aqueous phase by a layer of ~ 7–10 nm with a dielectric constant $\varepsilon < 82$ [48][49]. The "proton motive force" exerted by Respiratory Complex I is difficult to formulate in thermodynamic/mathematical terms. This coupling can be traced back to *localized coupling* which has already been proposed [50][51][52][53] as an alternative to *delocalized coupling* and is based on the rigid separation of the processes that occur in the membrane from those that occur in the aqueous phase.

4. Two phases of OXPHOS and Basics of Membrane's Proton Capacitor

Having established that the proton movement characteristic of OXPHOS is confined exclusively to the membrane and that the protons move thanks to the polar residues of the phospholipids which are located on the sides of the membrane bilayer, it is intuitive that these groups can express a buffer function [19], that is, they can retain protons in one phase to release them in a subsequent phase which leads to the rotation of the Fo subunit of the ATP Synthase with consequent ATP synthesis.

This function of membrane is called "Proton Capacitor" and to configure it's function is necessary to assume that OXPHOS can occur in two phases, as has been proposed for sleep [12] and generally for the course of OXPHOS so much so that an intermediate energy accumulator and its division into two phases has already been proposed [54].

Figure 3A shows the scheme of the Oxidative Phase, with proton translocation (performed by Respiratory Complex I) from the polar groups of the phospholipids facing the matrix to the polar groups of the phospholipids facing the intermembrane space. Figure 3B reports the scheme of the ATP Synthesis phase, with the protons passing from the polar "heads" of the phospholipids, facing to intermembrane space, to the polar "heads" of the phospholipids facing the matrix. The ATP Synthesis phase

is operative in the presence of ADP + Pi in the matrix, while in their absence the OXPHOS is limited to the Oxidative Phase with accumulation of protons in the dissociable groups of the membranes.

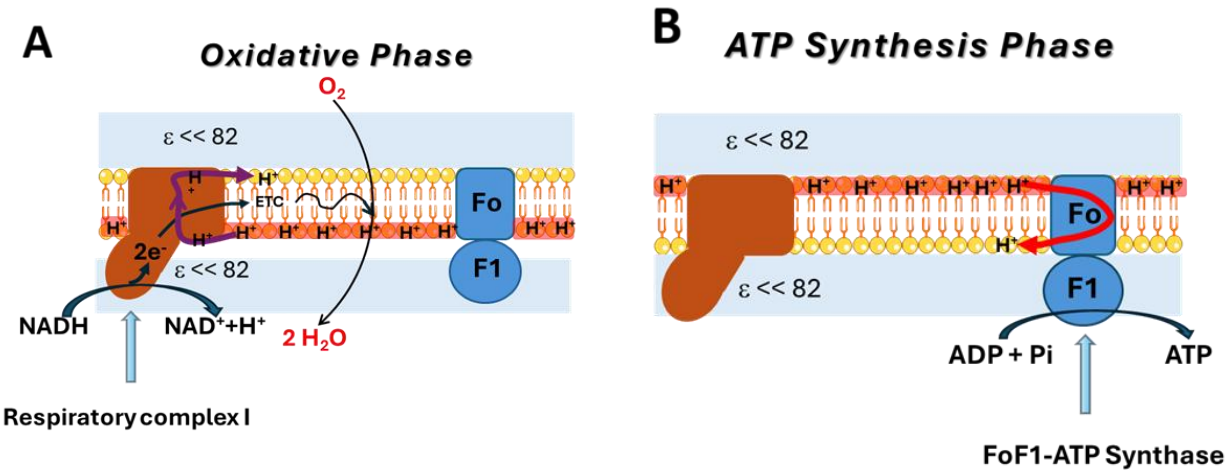


Figure 3. The diagram of the phases that lead to the "charging" and "discharging" of the proton capacitor is shown. For simplicity, only Respiratory Complex I is considered, which oxidizes NADH by initiating the Electron Transport Chain (ETC), coupled with the transfer of 4 H+ for each molecule of NADH oxidized. Fig. 3A provides the scheme of the "Oxidative Phase": the protons accumulated in the ionic group of phospholipid hemi-layer facing the matrix are transferred to the ionic group of phospholipid hemi-layer facing the intermembrane space and there they accumulate. Fig. 3B provides the scheme of the "ATP Synthesis Phase": the protons accumulated in the ionic group of phospholipid hemi-layer facing the intermembrane space are transferred to the ionic group of phospholipid in the hemi-layer facing the matrix passing through the Fo subunit with consequent it's rotation and transmission a molecular constriction to the F1 subunit that synthesizes ATP in the matrix.

The capacitance of the proton capacitor can be increased by the contribution of membrane proteins that can function as proton buffers as they contain numerous dissociable acidic groups [55]. This is the case of myelin which contains high amounts of Myelin Basic Protein (MBP) and proteolipid (PLP) which provide a notable increase in the proton capacitance of the myelin sheath, as has been roughly calculated [12]. Figure 4 shows the functioning of the proton capacitor that supports the sleep/wake cycle: the sleep phase corresponds to the oxidative phase, already described here in mitochondria, and is characterized by a proton pathway represented by the red line, while the wake phase, corresponding to the mitochondrial ATP synthesis phase, is represented by the purple line.

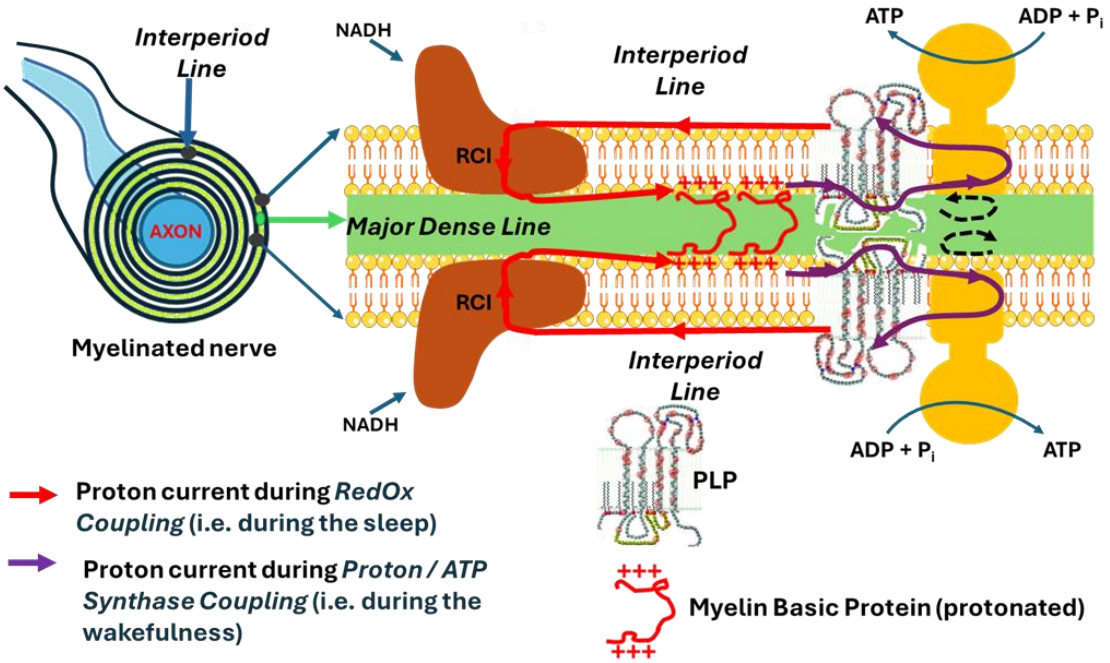


Figure 4. Scheme of proton capacitor function in the myelin sheath to support the sleep/wake cycle. The myelin sheath surrounding the nerve is shown on the left and a detail of the arrangement of the membranes is shown on the right: the interperiod line is the area corresponding to the mitochondrial matrix, while the major dense line corresponds to the mitochondrial intermembrane space. **Red line** = "proton recharging" phase of myelin: protons are transferred by means of Respiratory Complex I from the basic domain of the PLP immersed in the interperiod line to the MBP and to the basic domain of the PLP, both immersed in the major dense line of myelin. **Purple line** = Myelin "proton discharge" phase with coupled ATP synyhesis: protons are transferred from the MBP and the basic domain of the PLP immersed in the major dense line to the basic domain of the PLP immersed in the interperiod line; the proton current flows through the Fo subunit of the ATP Synthase with the consequent ATP synthesis by the F1 subunit immersed in the interperiod line.

5. Thermodynamic evaluations

Referring to the schemes presented above, we evaluate the thermodynamics of the entire process. The reactions with their corresponding free energy variations are as follows:

1) $2\ NADH + 2\ H^+ \rightarrow 2\ H_2 + 2\ NAD^+$ $\quad DG° = -\ 22.1\ KJ$

2) $O_2 + 4\ e^- + 4\ H^+ \rightarrow 2\ H_2O$ $\quad DG° = -\ 474.2\ KJ$

3) $2\ NADH + 2\ H^+ + O_2 \rightarrow 2\ NAD^+ + 2\ H_2O$ $\quad DG° = -\ 496.3\ KJ$

Equation 1) refers to the oxidation of 2 moles of NADH, which sets in motion 4 electrons that travel along the ETC until they discharge onto the O_2 molecule, producing 2 molecules of H_2O.

Equation 2) refers to the subsequent discharge of 4 electrons onto the O_2 molecule, producing 2 molecules of H_2O. The sum (3) cancels out 4 electrons + 4 H^+ from equation 2) with 2 H_2 from equation 1). Conventionally, one refers to one reduced oxygen atom producing one molecule of H_2O, so the DG° in equation 3) is divided by 2. Therefore, the DG° relating to one oxygen atom is DG° = - 496.3 : 2 = - 248.2 kJ. The protons set in motion for 1 NADH oxidized are 4 from Respiratory Complex I (NADH dehydrogenase), 3 from Respiratory Complex III (cytochrome c oxidoreductase) and 4 from Respiratory Complex IV (cytochrome c oxidase) for a total of 11. The stoichiometry of protons transferred by the Respiratory Complexes just cited refers to an authoritative contribution [56].

For many species, the complete rotation of Fo requires 8 protons, as many as the c subunits that make up Fo [57], therefore 11 protons ensure 11/8 = 1.38 rotations of the Fo subunit. Each rotation produces 3 ATP from the F1 subunit, therefore with 11 protons we will have the synthesis of 1.38 x 3 = 4.12 ATP. Each ATP involves a DG° = 30.5 KJ therefore the energy recovered in the form of ATP is 30.5 x 4.12 = 125.7 KJ. A theoretical efficiency of h = 125.7 : 248.2 = 51% is obtained which is within those predicted with other methods [58].

6. Conclusions and outlook

The traditional statement "*The Mitochondria are the Powerhouse of the cells*" can be amplified into "*The Mitochondria are exporters to the cell of the Power Molecular Machinery"* because it assemble the numerous proteins that carry out Oxidative Phosphorylation (OXPHOS) which through vesiculation they transfer to other cellular and extracellular sites making them able to synthesize ATP on their own. Furthermore, it appears that extra-mitochondrial ATP synthesis is widespread both within the cell and in the body's circulation due to the diverse presence of MDV.

All this requires overcoming the chemiosmotic theory [38][59][60][61] [62] [63][64] [65] and so the Proton Capacitor theory has now been formulated which foresees a clear division between the processes that occur in the membrane and those that occur in the aqueous phase that laps both sides of the inner mitochondrial membrane or other cellular membranes where OXPHOS is operative. The extra-mitochondrial OXPHOS have been found in the plasma membrane [66] [67] [68] [69] [70] [71] [72], in the endoplasmic reticulum [73][74], in the sarcoplasmic reticulum [11] and in the widely spread MDVs [29][75][28][16].

It goes without saying that this new approach greatly simplifies the original chemiosmotic theory because i) the processes involved occur only in the proteolipidic phase of the membrane and ii) it offers a new interpretation of the variation of the fluorescent signal generated by the so-called "membrane potential indicators" which with good reason reflect the degree of protonation of the membrane itself, as has been pointed out [19].

The import-export process of the OXPHOS molecular machinery has recently been outlined in the article "*Mitochondria-derived vesicles: potential nano-batteries to recharge the cellular powerhouse*" [17] and introduces the concept of "batteries" which is reminiscent of the possible existence of the "Proton Capacitor" which has already been described as the fulcrum around which the accumulation of energy in the form of protons revolves which are incorporated into the acid/base buffers of the membrane whose function has been proposed to formulate a coherent theory of sleep [12]. Furthermore the existence of the proton capacitor in membranes also depends on the formation of inverted micelles which increase the proton storage capacity [63].

The capacity of membranes to store protons, and therefore energy, is greater the larger the developed surface area of the membrane and this appears to be an evolutionary advantage accumulated by mitochondria which have developed, unlike the bacteria from which they derive, an internal membrane folded into cristae with the consequent increase in surface area for the same volume.

Interestingly, the sleep hypothesis requires a theory of OXPHOS functioning that coincides with the proton capacitor theory illustrated here, and this result may pave the way for understanding energy homeostasis in those energy-intensive organs, such as the heart, skeletal muscle, and kidneys, where extramitochondrial OXPHOS is highly active.

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