MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION: REMARKS ABOUT THE MECHANISM

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Smith and Hansen (1964) have reported that the flow of two electrons (in the form of $2e^-$ or $H:^-$ or $2H^\bullet$ or $H^\bullet + e^-$) from organic substrate down the mitchondrial electron transfer chain to oxygen is coupled to the phosphorylation of as many as six molecules of adenosine diphosphate (ADP) to produce a like number of molecules of adenosine triphosphate (ATP). Previous evidence had suggested that no more than three ATP's were generated in this manner. The increased efficiency of conversion of chemical energy released by mitochondrial electron flux into the chemical energy of the ATP - H_2O system can be interpreted to mean, as pointed out by Smith and Hansen, that more phosphorylation sites are present along the electron transfer chain than had previously been supposed, or that phosphorylation is coupled to one-electron transfer, rather than two-electron transfer, at some or all phosphorylation sites. In the present paper I shall make a suggestion regarding the mechanism of the possible coupling of one-electron transfer and phosphorylation.

Most chemically specific mechanisms which have been variously proposed in the literature to account for the coupling of electron flux over a phosphorylative segment of the transfer chain and the synthesis of an ATP molecule can be more or less precisely summarized by the generalized formulation shown in Fig. 1. The electron flux is shown to proceed from a carrier labeled A_n to the next carrier, A_{n+1}, both on the transfer chain. A chemical transformer, which may or may not be the same substance at different phosphorylation sites, mediates the coupling. The effective portion of the transformer molecule is represented by H-Y=Z, where Y=Z may symbolize not only a function with a true or formal double bond but also a conjugated

system in full or in part. No restriction to zero charge is implied for H-Y=Z. While most, if not all, of the steps shown in this and subsequent figures are reversible, it is pictorially simpler to show the arrows pointing only in the direction conducive to phosphorylation. The generalized mechanism may require considerable modification, but not a fundamental change, to suit an individual transformer.

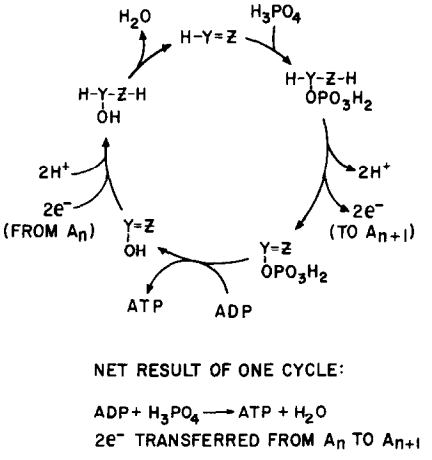

Fig. 1. Generalized mechanism for the coupling of phosphorylation to two-electron transfer.

Clearly the generalized mechanism shown in Fig. 1. requires a two-electron transfer through the phosphorylation site in order for one ATP to be generated. However, by the simple expedient to be described it becomes possible for a one-electron transfer to be coupled, by essentially the same general mechanism, to the formation of one ATP, provided, of course, that the energy drop suffered by one electron on passing from A_n to A_{n+1} is at least equal to the energy of formation of ATP + H_2O from ADP + H_3PO_4. The simple expedient is the availability of an electron depot which can, so to speak, furnish a second electron on loan. Thus, while two electrons pass through the phosphorylation site, only one undergoes net migration from A_n to A_{n+1}. For such depot activity the iron ion (ferrous⇄ferric) or the copper ion (cuprous⇄cupric) appears well suited. The operation of the electron depot would no doubt be greatly facilitated, especially with regard to timing, if the involved iron ion or copper ion were bonded to the transformer molecule throughout the various stages of the cyclical mechanism. The generalized

formulation presented in Fig. 2. incorporates the suggested role of an electron depot as exemplified by the iron ion.

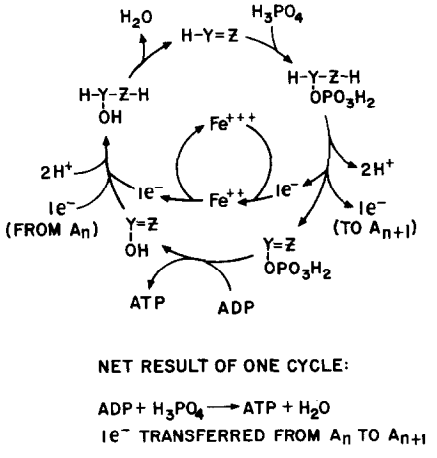

Fig. 2. Generalized mechanism for the coupling of phosphorylation to one-electron transfer. Copper ion (cuprous⇄cupric) may replace iron ion (ferrous⇄ferric) as electron depot.

I do not wish to speculate on substances which might play the transformer role or to express a preference for any literature proposals, but a concrete illustration of my suggestion is appropriate. In Fig. 3. is shown a mechanism in which histidine (protein-bound) functions as transformer in the presence of an electron depot as exemplified again by the iron ion. One may expect the iron ion or copper ion which performs as electron depot to be coordinatively bonded to the imidazole nucleus. As a matter of background, Boyer et al. (1962) reported the isolation of a protein-bound phosphohistidine (phosphoryl group attached to an imidazole nitrogen) from mitochondrial preparations, and on the basis of this and further work Boyer (1963) discussed the possible transformer activity of protein-bound phosphohistidine.

Obviously, if the electron depot (iron ion or copper ion) were absent from the mechanism of Fig. 3., then two electrons, instead of one, would be transferred from A_n to A_{n+1}, i.e. both electrons freed on dehydrogenation of the imidazole ring -

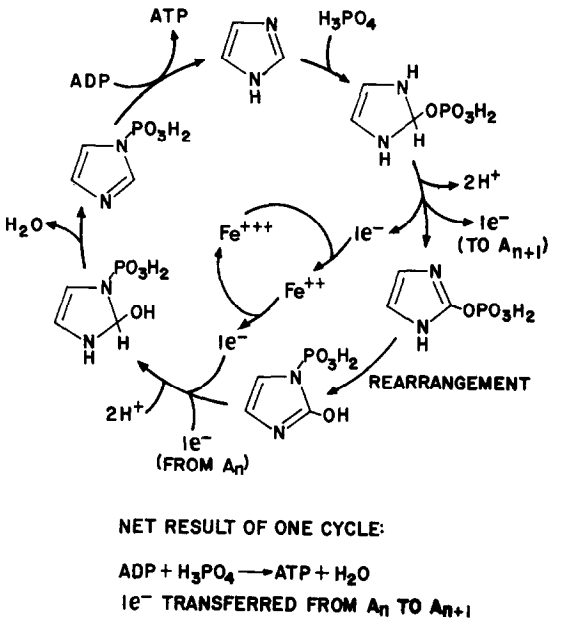

Fig. 3. Mechanistic suggestion for the possible coupling of phosphorylation and one-electron transfer by the transformer action of histidine (protein-bound) in the presence of an electron depot as exemplified by iron ion. Only the imidazole ring of histidine is shown. This mechanism serves as illustration and is not an expression of preference for histidine over other possible transformers.

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phosphoric acid adduct would go to A_{n+1} and both electrons required for hydrogenation of the 1-phospho-2-hydroxyimidazole structure would come from A_n.

REFERENCES

Boyer, P. D., Science, 141, 1147 (1963).
Boyer, P. D., DeLuca, M., Ebner, K. E., Hultquist, D. E., and Peter, J. B., J. Biol. Chem., 237, PC3306 (1962).
Smith, A. L., and Hansen, M., Biochem. Biophys. Res. Comm., 15, 431 (1964).