Coherent Properties of Energy-Coupling Membrane Systems

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1 Introduction and Scope

An understanding of the organization of biological systems is predicated upon an understanding of their energetics. Thus the present chapter will give a very broad overview of some of the current thinking in bioenergetics, with especial reference to the formation of ATP linked to the transport of electrons down their electrochemical potential gradient, as catalyzed by biomembranes containing mobile protein complexes participating in the two half-reactions (Fig. 1). Here we see how the downhill reactions of electron transport are coupled to the otherwise endergonic ATP synthase reaction through the transfer of one or more quanta of free energy (Fig. 1A). Arguably, the major problem of bioenergetics concerns the nature of this free-energy-transducing quantum, and Fig. 1B shows some of the salient possibilities under discussion (Kell and Harris 1985a). Only the celebrated chemiosmotic model may be regarded as reasonably well developed (Nicholls 1982; Harold 1986), but since its perceived shortcomings have been discussed elsewhere in extenso (e.g. Ferguson and Sorgato 1982; Kell 1979, 1986a, 1987a, 1988; Ferguson 1985; Kell and Hitchens 1983; Westerhoff et al. 1984a; Kell and Westerhoff 1985), I shall not concentrate on it in detail here, where a more heuristic overview is appropriate.

One distinction to be made between various approaches to describing energy coupling in electron transport-linked phosphorylation (ETP) is whether the intermediates they postulate for such a process are or are not thermally activated (Blumenfeld 1983; Welch and Kell 1986; Kell 1987b, 1988). For this reason, and in view of the subject matter of the present volume, I shall devote my space to describing how in principle we should best seek to treat an energy-coupling system, and to reviewing some recent studies which have sought to estimate the degree of coherence involved in such processes. As before (Kell and Hitchens 1983; Kell and Westerhoff 1985; Kell 1988), I shall take "coherence" to cover the idea that the motions of one or more parts of a system are directly and functionally linked to those in a spatially separate part of the system, so that free energy may be transferred between them in an essentially dispersionless fashion.

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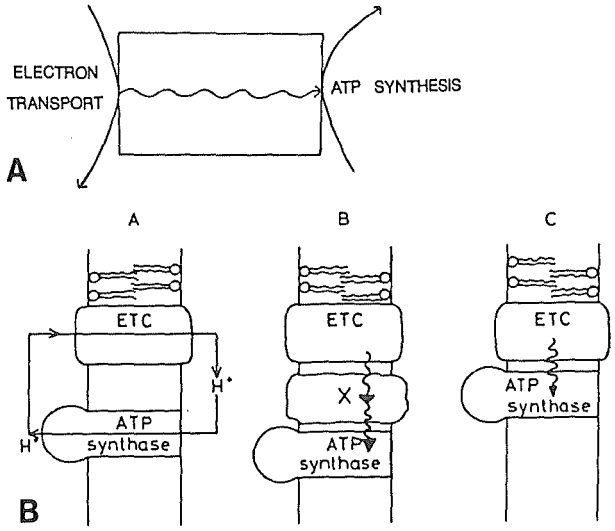

Fig. 1. A The central problem of energy coupling in electron transport-linked phosphorylation. The system is modelled as a black box in which the input reaction is electron transport catalyzed by a particular enzyme complex whilst the output reaction is ATP synthesis catalyzed by a separate enzyme complex. Free energy *(wiggly line)* is conserved by the first enzyme and passed to the second enzyme. Both enzymes are embedded in a so-called energy coupling membrane. B Three possible models for this process: in the chemiosmotic model *A*, the electron transfer complex *(ETC)* pumps protons across the membrane; these protons may return to the aqueous phase in which they originated by means of a proton-translocation ATP synthase. The lateral mobility of these complexes is irrelevant. By contrast (*B*, *C*) a special arrangement of the ETC and ATP synthase complexes may be necessary to effect free energy transfer by means of an unknown energised state, involving electrical and acoustic modes of the membrane (proteins). There may (*B*) or may not (*C*) be a requirement for other proteins (*X*) to participate in this energy coupling

2 Conformational States of Protein Molecules

A typical protein of molecular weight 20 kD may possess or explore some 10^{80} conformational substates (e.g. Jaenicke 1984). However, even if we let it explore them at a rate of 10^{15} per second, it cannot possibly explore all of those available in passing from a given conformational "state" to another, since the Universe is "only" some 10^{17} s old (Barrow and Silk 1983). Thus even an isolated protein, ostensibly in equilibrium with a heat bath, is not an ergodic system. Nonetheless, it is usual to speak of "the" structure of a protein, and the changes in angles and lengths of non-covalent intramolecular bonds caused by thermal energy (kT) are both relatively small and are observable in electron density maps obtainable by X-ray diffraction (e.g. Ringe and Petsko 1985). This allows us to make progress, but does not tell us if anything about whether something qualitatively different takes place when we allow our protein to do something, such as to catalyze the approach to equilibrium of a chemical reaction involving small molecules.

A consideration of typical free energy diagrams as drawn for enzymatic processes (e.g. Fersht 1985), in which the free energy of the system is plotted against the reac-

tion coordinate, indicates that enzymes are equilibrium thermochemical machines which may exploit (at least part of) the energy of ligand binding to lower, and facilitate passage over, the energy barrier separating the enzyme-substrate and enzyme-product complexes. But whilst these typical aqueous globular enzymes do transduce free energy in the sense that they attain (pass through) states with a higher free energy than the ground state, their macroscopic effect is, as stated, simply to catalyze the approach of a reaction to equilibrium. There is then no thermodynamic paradox here, despite the fact that our enzyme is acting isothermally, since it is only required that the overall ΔG for the system $\leqslant 0$ (Kemeny 1974; Lumry 1980; Cooper 1984; Somogyi et al. 1984). Indeed, the view that an enzyme acts at least in part as an "equilibrium chemodynamical machine" (Somogyi et al. 1984) has been significantly strengthened recently by the demonstration that an important partial reaction catalyzed by engineered derivatives of the *Bacillus stearothermophilus* tyrosyl-tRNA synthetase exhibit linear free energy relationships (Fersht et al. 1986). By contrast, studies by Frauenfelder and coworkers (Ansari et al. 1985) and by Isied and colleagues (Bechtold et al. 1986) have shown that even aqueous, globular proteins can apparently exhibit out-of-equilibrium states for considerable periods.

The problem then is (Welch and Kell 1986): how does an enzyme which, whilst it is fluctuating considerably about its "mean" conformation(s) [and hence free energy (Welch et al. 1982; Welch 1986; Englander and Kallenbach 1984)], succeed in distinguishing a conformational substate which is arrived at by means of a "favourable" set of thermally-induced fluctuations (and which it is not allowed to use to conserve free energy) from one which arises by virtue of a (macroscopically) thermodynamically favourable reaction such as ligand-binding (McClare 1971), since at the submolecular level they are in principle indistinguishable? Evidently, and whilst this is to an extent self-defining, the latter case is associated with regions of conformational phase space which are only rarely if ever encountered by the enzyme in its "ground state" ($\pm$ kT), and it must be taken that these regions of conformation space are characterized by the fact that collective and microscopically "irreversible" motions are required to attain them. It is the "rarely if ever" phrase in the previous section which gives us a further clue, since it immediately introduces the idea of time into thermodynamics, as required by our earlier simpler analysis indicating the impossibility that an ensemble of protein molecules could be an ergodic system even when at equilibrium in a heat bath. Thus our enzyme, by catalyzing a reaction in a "forward" direction, exhibits irreversibility de facto. Similarly, the fact that an enzyme obeys the Haldane relationship (see Fersht 1985) does not of itself prove that the forward and back reactions are mechanistically identical, merely that the free energies (chemical potentials) of the intermediates are. In this regard, it is worth remarking that an imperfectly coupled molecular energy machine catalyzing a reaction against the chemical potential of its ligands may be identified on the basis that it will *not* obey the Haldane relationship.

At the current state of knowledge we can say little more about this at the fundamental or even mechanistic levels, beyond indicating that the acceptance of this fact alone shows that protein molecules must exhibit collective or coherent *intra*molecular motions. A recent series of calculations of relevance to the present problem (Astumian et al. 1987; Westerhoff et al. 1986, 1987) shows that the electrical noise spectrum of a prototypical membranous energy-transducing enzyme is far from white, and that

such an energy transducer can harvest exogenous electrical energy (both sinusoidal and "noise") of mean free energy $< kT$, provided that the noise spectrum of the exogenous field is not complementary to that of the enzyme. This provides a reasonably simple and well-defined type of mechanism by which a membrane-located energy converter may apparently disobey the second law in its usual formulations (i.e. act non-thermally sensu lato), although other thermally based but non-linear mechanisms such as field-induced "lateral electrophoresis" (see Harris and Kell 1985; Kell and Harris 1985b; Kell 1987b; Pething and Kell 1987) might appear to possess similar properties under appropriate conditions. In a similar vein, a recent study by Careri and colleagues (1985) of the dielectric behaviour of lysozyme has shown a highly cooperative channelling of protons from sites along the enzyme's entire surface (with a 7th order dependence on the number of bound protons) towards the enzyme's active site.

Since macroscopically observable conformational states ("primary macroergs" in the terminology of Blumenfeld 1983) may persist at least for seconds in bioenergetics, some mechanisms must be operative to restrict, in a kinetic sense, the decay of these conformational states to equilibrium (with consequent heat evolution) whilst permitting, in appropriate cases, their conservation as "high-energy" conformational states within the same molecule or by transfer to another protein molecule. The latter is what bioenergeticists refer to as energy coupling, or, in Fröhlich's (1969) phrase, the ability of a system "very strongly to excite a few modes of motion".

Two major classes of mechanistic proposal for the existence in living systems of the types of behaviour alluded to above include a variety of the possible solitary excitations or solitons (see e.g. Webb 1980; Bilz et al. 1981; Blumenfeld 1983; Davydov 1983; Jardetzky and King 1983; Scott 1983; Careri and Wyman 1984; Del Giudice et al. 1984; Lomdahl 1984; Lomdahl et al. 1984; Somogyi et al. 1984) and Fröhlich's (1968, 1969, 1980, 1986; Fröhlich and Kremer 1983) theory of collective excitations in biological systems. All of these theoretical formalisms share the idea that particular metastable, high-energy (out-of-equilibrium) states of proteins in vivo may be created as intermediates in and by natural processes and thus may be created or destroyed by very weak (non-thermal) exogenous stimuli. Based upon evidence from inhibitor titrations inter alia (see Kell and Hitchens 1983; Kell and Westerhoff 1985; Herweijer et al. 1986; Kell 1986, 1987a; Pietrobon and Caplan 1986a,b; Petronilli et al. 1987; Westerhoff and Kell 1987), it appears that the membranous systems of electron transport phosphorylation possess precisely this property of a coherent or dispersionless transfer of free energy between the spatially separate but mobile complexes catalyzing the appropriate half-reactions of electron transport and of phosphorylation. The question then arises as to whether they might also be expected to respond to weak exogenous stimuli.

3 Response of Membrane Proteins to Exogenous Electrical Fields

The imposition of an exogenous, sinusoidal electrical field of peak-to-peak field strength E_0 V/m and frequency ω radians/s via two macroscopic electrodes between which are held a suspension of (spherical) membrane vesicles of radius r induces a transmembrane electrical potential $\Delta\psi$ given approximately (Tsong 1983) by:

$$\Delta\psi = (1.5\ E_0 r \cos\theta)/[1 + (\omega\tau)^2]^{1/2}\ , \quad (1)$$

where θ is the angle between a portion of the bilayer and the field direction and τ is the relaxation time for the charging of the membrane capacitance, i.e. the classical Maxwell-Wagner dielectric dispersion (see e.g. Kell and Harris 1985a; Pethig and Kell 1987). Generally these values of $\Delta\psi$ are tiny, and whilst the dipole moments μ of membrane proteins may be reasonably large, some several hundred Debyes (Neumann 1986; Pethig and Kell 1987), it is not expected that the Langevin factor $\mu E_0/kT$ (which determines the extent of any thermally based biological response) will attain any significant magnitude. Indeed, it is well known that induced DC values of $\Delta\psi$ of at least 150 mV are required to drive the synthesis of ATP by membranes incorporating an H^+-ATP synthase (see Kell 1986; Tsong and Astumian 1986). Since rather weak AC fields have been shown to elicit a plethora of biological responses in membranous systems (see e.g. Adey 1981; Pilla et al. 1983; Sepersu and Tsong 1984), however, it is evident that the idea of a membrane protein as a passive dipole is inadequate. In any event, both lipids and proteins are known not to undergo "flip-flop" motions (rotation about an axis in the plane of the membrane) on any time-scale of biological significance. By contrast, all types of proteins possess a marked fluctuational mobility, necessarily accompanied by (permanent and induced) dipolar changes, on a time-scale from picoseconds upwards (e.g. Gurd and Rothgeb 1979; Englander and Kallenbach 1984; Welch et al. 1982; Somogyi et al. 1984; Pethig and Kell 1987). Thus any membrane protein will be able to change its conformation(s) in response to an exogenous electrical field of virtually arbitrary frequency and magnitude, with a concomitant change in its enzymatic activity.

One explicit possibility, developed by Astumian, Tsong, Westerhoff and colleagues (see Westerhoff et al. 1986, 1987; Tsong and Astumian 1986) considers an ion-motive membrane protein as a machine which can exist in (at least) four dipolar states, each state being populated (and differentially liganded) to an extent dependent upon the number and nature of its bound ligands. Provided that these states are asymmetric, the protein will succeed in "harvesting" the free energy in the electrical field so as to drive a cyclic ion-pumping process even though the free energy in the field is apparently insufficient.

This simple example indicates one means by which a membranous enzyme might be affected by an electrical field. Similarly, whilst the fact that a protein is embedded in a membrane causes an "amplification" of the macroscopic electric field (see Tsong and Astumian 1986), this type of mechanism can work perfectly well for a "soluble" protein, particularly if its Debye-like rotation is restricted by its being bound to a cytoskeletal structure (or a cognate arrangement in a prokaryote). There has been some discussion of the ability of such structures to participate in energy transfer in vivo (e.g. Welch and Berry 1985), but whilst the existence and importance of such cellular organization is becoming well established (e.g. Clegg 1984; Welch 1985; Welch and Clegg 1987), experimental evidence for an energy-coupling role of these structures remains elusive.

That the activity of an enzyme may be affected by an exogenous parameter, such as the imposition of an electrical field, does not of itself mean that the flux of metabolites through a pathway of which the enzyme is a part will be similarly affected. This is because not all enzymes contribute to an equal extent to the control of flux.

Following the work of Kacser, Burns, Heinrich and Rapoport, the appropriate relationships between enzyme activities and pathway fluxes have been formalized in the so-called Metabolic Control Theory (for reviews see Westerhoff et al. 1984b; Kell and Westerhoff 1986a,b). This analysis provides a quantitative mechanistic description of the effects of an external variable on a steady-state metabolic system, and it is to be hoped that workers studying the effects of electrical fields on cells will adopt the formalism in the description of their experiments.

4 Concluding Remarks

What I hope to have been able to convey in this short overview is (a) that proteins, as complex macromolecules, must exhibit collective motions by virtue of their structures and the ambient thermal energy; (b) that non-thermally excited states may also be achieved and persist for periods that are long relative to those exhibited by simple molecules in viscous media; (c) that the distinction between these types of states is conceptually difficult and to an extent self-defining; (d) that both soluble and membranous proteins may absorb electromagnetic radiation which may affect both their kinetics and energetics, even when the free energy in the exciting field is miniscule; and (e) that the imposition of exogenous electrical fields of virtually arbitrary magnitudes and frequencies will lead to biological effects, but not necessarily in proportion to the change in turnover number of the "target" enzymes. On a more applied note, this opens up the possibility, despite a long history of empiricism (Rowbottom and Susskind 1984), of what really represents an entirely novel approach to affecting selectively the metabolism of living systems (Kell 1987c), both for good and for ill (Becker and Marino 1982; Becker and Selden 1985; Marino and Ray 1986), and one which we may hope might lack the side-effects of current chemotherapies.

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