Dimers are forever: New developments in the mechanism of the Na^+,K^+-ATPase

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The Na^+,K^+-ATPase (or sodium pump) was the first ion pump to be discovered (Skou, 1957) and it is one of the most fundamentally important enzymes of animal physiology. The electrochemical potential for Na^+, which the enzyme maintains, is used as the driving force for numerous secondary transport systems, *e.g.*, voltage-sensitive Na^+ channels in nerve. The mechanism of the Na^+,K^+-ATPase is universally described in biology textbooks by the Albers-Post cycle, which represents the catalytic subunit of the enzyme as a monomer undergoing a cyclical sequence of conformational changes, ion binding and release steps and ATP phosphorylation/dephosphorylation reactions. Although this mechanism is consistent with the vast majority of experimental data, for many years research groups around the world have discovered reproducible results which are inconsistent with this mechanism: 1) multiple ATP binding affinities; 2) phosphorylation of half of the ATP binding sites; 3) simultaneous presence of two intermediate states of the cycle; and 4) two-step release of K^+ ions. These inconsistencies indicate that the widely accepted Albers-Post model cannot be the full truth. The results of stopped-flow kinetic experiments and theoretical simulations (Clarke & Kane, in press) indicate that the enzyme exists as a functional dimer within the membrane. To explain these results as well as previous inconsistencies with the Albers-Post model, we propose a new mechanistic model in which the enzyme cycles at a low rate with ATP hydrolysis by one catalytic subunit or at a high rate with ATP hydolysis by two catalytic subunits simultaneously within a dimer, depending on the concentration of available ATP. Thus, we propose a bicyclic model with two gears to replace the classical monomeric Albers-Post cycle.

Skou JC. (1957) *Biochimica et Biophysica Acta*, **23:** 394-401.
Clarke RJ & Kane DJ. (2007) *Biophysical Journal*, in press.