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This Week's Citation Classic

Skou J C. Enzymatic basis for active transport of Na^+ and K^+ across cell membrane. *Physiol. Rev.* **45**:596-617, 1965.
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The paper is a review on the characteristics of a membrane bound $Na^+ + K^+$ activated ATPase which shows that the system is responsible for the energy requiring transport of Na^+ and K^+ across the cell membrane. [The *SCI®* indicates that this paper has been cited over 1,580 times since 1965.]

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"In the beginning of the 1950s I was interested in the effect of local anaesthetics (l.a.) and had found that the increase in surface pressure by penetration of local anaesthetics into a monolayer of lipids extracted from nerves correlated to their local anaesthetic effect. This raised the question: Can an increase in surface pressure from penetration of l.a. into the lipid part of a nerve membrane influence the configuration of proteins in the membrane and thereby block the trigger mechanism in the Na^+-channels? Experiments showed that the activity of surface spread enzymes (catalase and acetylcholin esterase) was surface pressure dependent which was taken as an indication of an effect of surface pressure on protein configuration. I then needed a monolayer of a lipoprotein with enzyme activity to test the effect of penetration of l.a. Libet[1] had shown that there is an ATPase in the sheath part of giant axons, and being membrane bound it was likely that it was a lipoprotein. I had no access to giant axons but looked for and found an Mg-ATPase in the microsomal fraction from a homogenate of crab nerves. However, activity varied from preparation to preparation and with no explanation. Finally after three months of work it was observed that K^+ in the test solution increased activity. I went on a summer holiday to forget about ATPases and crab nerves. After returning, the experiment was repeated but no effect of K^+ was found. However, addition of Na^+, which had little or no effect in the presence of Na-ATP, increased the activity when K-ATP was used, i.e., the activity was $Na^+ + K^+$ dependent. This explained the varying results. Sometimes Na^+ and sometimes K^+ had been used for ionic strength effect in the buffer and as counter ion for ATP. The characteristics of the system suggested that it was involved in active transport of Na^+ and K^+ across the cell membrane. This shifted my interest to active transport of cations. The results were published in 1957.[2]

"Crab nerves were a lucky choice and later experiments showed that it is one of the few tissues where the Na, K-ATPase activity is revealed without use of detergents. A problem was, however, to kill the crabs, 25,000 shore crabs–200,000 nerves. The only usable way was to put them in boiling water immediately after having cut the legs –but the smell! 'Couldn't you use another tissue,' was a standing remark in the department.

"The often cited paper is a review on the following eight years of research on the Na,K-ATPase by many different authors which gave the evidence that the enzyme is found in the membrane of most cells and is responsible for the active transport of Na^+ and K^+ across the cell membrane. It appeared at a time when membranes had come into focus and there was a lot of interest in cations. For more recent information and references see, 'Isolation and characterization of the components of the Na^+ pump' and *Na,K-ATPase, Structure and Kinetics.*"[3,4]

1. **Lilbet B.** Adenosinetripbosphatase (ATP-ase) in nerve. *Fed. Proc.* **7**:72-3, 1948.
2. **Skon J C.** The influence of some cations on the adenosine triphosphatase from peripheral nerves. *Biochim. Biophys. Acta* **23**:394-401, 1957.
3. **Jørgensen P L.** Isolation and characterization of the components of the Na^+ pump. *Quart. Rev. Biophys.* **7**:239-74, 1975.
4. **Skou J C & Nørby J G ,** eds. *Na,K-A TPase, structure and kinetics.* London: Academic Press, 1979. 549 p.