

This Week's Citation Classic™

Schatzmann H J. Herzglykoside als Hemmstoffe für den aktiven Kalium- und Natriumtransport durch die Erythrocytenmembran. (Cardiac glycosides as inhibitors for the active potassium and sodium transport across the red cell membrane.) *Helv. Physiol. Pharmacol. Acta* 11:346-54, 1953. (Pharmakologisches Institut. Universität Bern. Switzerland)

It was shown that k-strophanthoside (10^{-5} g/ml) and the aglycones strophanthidin and digitoxigenin completely block the uphill Na^+ and K^+ movements in human red cells and that this inhibition is likely to be due to a direct effect on the $\text{Na}^+ - \text{K}^+$ pump. [The SCI® indicates that this paper has been cited in over 620 publications since 1955]

H.J. Schatzmann Department ,of
Veterinary Pharmacology
University of Bern 3000
Bern, Switzerland

July 10, 1984

"After graduating from medical school, I worked in the Bernese Department of Pharmacology with W. Wilbrandt. With a primordial flame photometer (run in complete darkness and going awry every so often), I observed the red cell $\text{Na}^+ - \text{K}^+$ pump. Its existence, at the time, was something more than a lingering feeling and less than a textbook truth.¹

Wilbrandt suggested that min-eralocorticoids should be tested on it, the idea being that they supplied the ionophoric group. Intracellular receptors for steroids and their effects were unknown, and the idea seemed worth examining. I tried it—in vain.

"It was known that Na^+ reduced the force of the heart,² but the $\text{Na}^+ - \text{Ca}^{++}$ exchange system not having been discovered yet, one could think that internal Na^+ was responsible. My loose thinking went as follows: steroid hormones stimulate $\text{Na}^+ - \text{K}^+$ transport (in the kidney); cardiac glycosides are steroids and might be cardiotonic by virtue of a similarity with steroid hormones. Unaware of the structural differences between the

two, I exposed my red cells to strophanthoside, hoping that it would do what the corticoids failed to do. The inhibitory action was soon obvious. Thus, by looking for a steroid requirement, I had found an inhibitor; the three princes from Serendip smiled.

"Strophanthoside clearly did not ruin transport by causing a leak. To decide whether the inhibition acted on the pump or the energy supply, I measured glycolysis in a Warburg apparatus (another exasperating machine; Wilbrandt kept telling me that it was 'the very model Sir Hans Krebs was using'). There was no reduction of glycolysis, and I drew the correct conclusion, namely, that the inhibition acted directly on the pump. Whittam *et al.*³ later showed that the experiment was not good enough. (A drop in glycolysis [by 15 percent] follows whenever the pump is stopped.)

"The discovery produced some interest probably for two reasons. First, owing to extreme specificity, cardiac glycosides identify whatever is connected to the $\text{Na}^+ - \text{K}^+$ pump.⁴

abnormal modes (reverse, exchange, uncoupled Na flux) as well as secondary transports. With their help, Skou's $\text{Na} + \text{K} + - \text{ATPase}$ ⁵

was easily recognized as the $\text{Na} + - \text{K}^+$ pump. Second, the finding fostered the hope that the mechanism of the positive inotropic action of cardiac glycosides, elusive as it was, was around the corner.⁶

"These scientific pursuits were pleasantly punctuated by little excitements. One day, an undesirable spatial arrangement between a lit Bunsen burner and the dustcover (a piece of pink cotton) set the flame photometer ablaze when nobody was present. Wilbrandt had the bad luck to step into the room when the spectacle was at its best. He fought the conflagration successfully without the convenience of a CO_2

fire extinguisher. Unsuspecting, I met him a minute later in the hall, dishevelled, agitated, and with a charred blanket in his hands. He did not conceal his disapproval of what he called an unduly literal interpretation of the word 'Flammenphotometer.'"

1. Maizels M. Factors in the active transport of cations. *J. Physiol.—London* 112:54-83. 1951. (Cited 160 times since 1955.)

2. Wilbrandt W & Koller H. Die Calciumwirkung am Forscherherzen als Funktion des Ionengleichgewichts zwischen Zellmembran und Umgebung. *Helv. Physiol. Pharmacol. Acta* 6:208-21. 1948. (Cited 145 times since 1955.)

3. Whittam R, Ager M E & Wiley J S. Control of lactate production by membrane adenosine triphosphatase activity in human erythrocytes. *Nature* 202:1111-12. 1964.

4. Glyan I M. The action of cardiac glycosides on ion movements. *Pharmacol Rev* 16:381-407. 1964. (Cited 545 times.)

5. Skou J C. The influence of some cations on adenosine-triphosphatase from peripheral nerve. *Biochim. Biophys. Acta* 23:394-401. 1957. (Cited 1,205 times since 1957.)

6. Akera T & Brody T M. The role of $\text{Na}^+ . \text{K}^+ - \text{ATPase}$ in the inotropic action of digitalis. *Pharmacol. Rev.* 29:187-220. 1978. (Cited 150 times.)