letter to the editor

Remarks on the nature of ion-ion interactions in channels, as presented by Wu

To explain the "multi binding site" behavior of the potassium channel, Jin V. Wu argued in his paper: "Dynamic ion-ion and water-ion interactions in ion channels" (1), that the kinetic energy and the inertial mass in general is a major factor in the ion-ion displacements (knock-off's) at the channel binding site. This argument has, however, the severe flaw that the kinetic energy $\frac{1}{2}mv^2$ even of a very heavy ion ($M = 200$) at the highest thinkable velocity within the membrane of $\sim$200 cm/s for a local electric field of 10^6 V/cm is three to four orders of magnitude smaller than kT. It is inappropriate to assume as done by Wu that the short range collision free speed is equal to the surface escape velocity $V = (8\,\mathrm{kT}/\pi m)^{1/2}$ when the mean free path in the free volume approaches zero. Moreover the Maxwellian velocity distribution implies that one molecule is kicked up to its velocity by collision with other molecules of comparable velocities. In the liquid states the long or short range velocities of all the molecules are determined by the hydrodynamic resistance or viscosity and the Maxwellian velocity distribution is centered around the velocity determined by the hydrodynamic properties of the solution. Is the implication of the mass really required in order to resolve the following paradoxes pointed out by Wu: Why is conductance of K^+ in a K^+ channel higher than that of Tl^+ in symmetrical solutions while in bionic solutions the permeability of Tl^+ appears to be higher than that of K^+ as determined by reversal potential? Does the higher binding affinity of ions of equal radii and higher masses mean that the inertial mass is involved or that the mass affects other properties, e.g., ionic polarizability (deviation of the charge from the ionic center)?

The "paradoxical" phenomena of the higher permeability of K^+ than that of Tl^+ in pure salts and higher permeability of Tl^+ in salt mixtures can be explained without invoking the ion masses or any fictitious kinetic energies. The qualitative description is as follows: Ionic association or ion pair formation is by and large a diffusion controlled process. An ion with a higher affinity to a site has, therefore, a slower dissociation rate. This dissociation rate is usually the rate controlling step in ion channel permeability and therefore the permeability in pure salts of the faster dissociating K^+ is higher than of the slower dissociating Tl. To the scheme on page 1319 of reference 1 for the case of a symmetrical pore:

$$O + A_1 \underset{K_2}{\overset{K_1}{\rightleftarrows}} OA \underset{K_1}{\overset{K_2}{\rightleftarrows}} O + A_2,$$

a second scheme is to be added for the case that most binding sites are occupied and the bound ion is knocked off by an ion impinging from the solution via formation of a transition complex

$$A_1 + OA \underset{K_4}{\overset{K_3}{\rightleftarrows}} AOA \underset{K_3}{\overset{K_4}{\rightleftarrows}} OA + A_2.$$

The two schemes for the case of a symmetrical channel are also depicted in Fig. 1. The knock off reactions by the ion coming from the opposite direction and the ordinary dissociation reactions are affected by different factors, e.g., steric considerations, local dielectric constant and presence of water, which determine the variation of the electrostatic interaction energy in course of the exchange reaction, etc. The knock off reaction has to go through a transition complex depicted in Fig. 1. The energy of the transition (activation) complex determines the rate of the exchange reaction.

For the transfer of ion A from side 1 to side 2 through the pore it has to form first the ion pair OA at a rate $K_1[\mathrm{O}][A_i]$ and then to dissociate to side 2 either spontaneously $K_2[OA]$ or to be knocked off by A_1 at a rate $K_3A_1(OA)$. Similarly with respect to the transfer from side 2 to side 1. Bearing in mind that OA is formed by Scheme I from $A1$ and $A2$ proportionally to their concentration, the flux ratio from side 1 to side 2 to that in the opposite direction, is given by

$$\frac{J_1}{J_2} = \frac{A_1(K_3A_1 + K_2)}{A_2(K_3A_2 + K_2)}.$$

One can apply a similar argument for two ions competing for the same binding site. With K_{1A}, K_{1B}, K_{2A}, K_{2B} the association and dissociation rate constants of ions A and B and with K_{AB}, K_{BB}, K_{AB} and K_{BA} the knock off rates of ion A by A, B by B, A by B, and B by A, the flux ratios J_{1A}/J_{2A}, J_{1A}/J_{1B}, etc., acquire the following forms:

$$\frac{J_{1A}}{J_{2A}} = \frac{(K_{2A} + K_{AA}A_1 + K_{AB}B_1)A_1[K_{1A}K_{AB}A_1 + K_{1A}K_{1B}(B_1 + B_2) + K_{1A}K_{2B} + K_{1B}(K_{AB} - K_{1A})(B_1 + B_2)]}{(K_{2A} + K_{AA}A_2 + K_{AB}B_2)(A_2[K_{1A}K_{AB}A_2 + K_{1A}K_{1B}(B_1 + B_2) + K_{1A}K_{2B} + K_{1B}(K_{AB} - K_{1A})(B_1 + B_2)},$$

$$\frac{J_{1A}}{J_{1B}} = \frac{(K_{2A} + K_{AA}A_1 + K_{AB}B_1)A_1[K_{1A}K_{AB}A_1 + K_{1A}K_{1B}(B_1 + B_2) + K_{1A}K_{2B} + K_{1B}(K_{AB} - K_{1A})(B_1 + B_2)]}{(K_2B + K_{BB}B_1 + K_{BA}A_1)B_1[K_{1B}K_{BA}B_1 + 1_{1A}K_{1B}(A_1 + A_2) + K_{1B}K_{2A} + K_{1A}(K_{BA} - K_{1B})(A_1 + A_2)}.$$

If the affinity of B to the site is larger than that of A then the expected relative values of the rate constants are as follows: $K_{AB} > K_{BB} > K_{BA}$. However, the spontaneous dissociation rate constants $K_{2A} > K_{2B}$ and the symmetric knock offs $K_{AA} > K_{BB}$. With all this in mind it is easy to show that these simple equations can fully represent the "paradoxical" behavior including the difference in conductances of solutions containing one binding ion or two ions with different activities and the deviation from the Michaelis-Menten behavior at high ionic activities.

This does not mean that water molecules do not play a role

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in the knock off reactions and dissociation rates. They do it as competitors for binding and affecting the local dielectric constants but not through their mass or kinetic energy.

To sum up: Any implication of inert mass or kinetic energies of ions or water molecules is neither justified nor necessary to explain the kinetics of channel conductance.

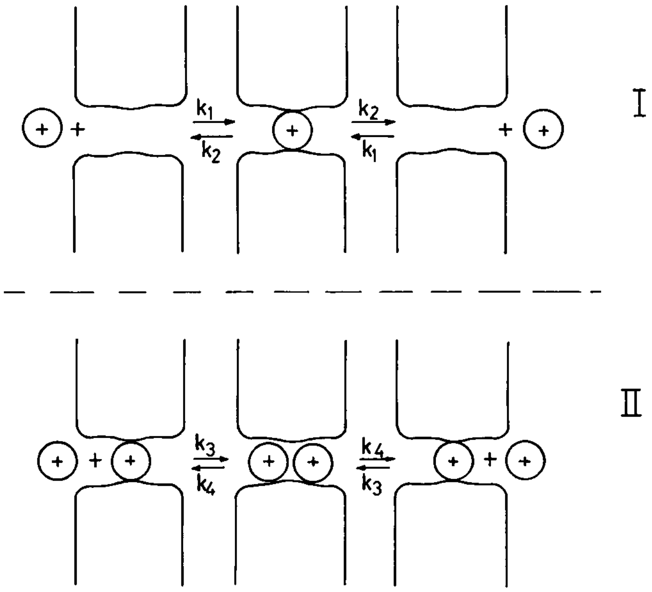

FIGURE 1 Model of a symmetric cation channel with a binding site. (*Scheme I*) Binding to a free site and dissociation from it. (*Scheme II*) Displacement of an ion from the binding site by an ion of the same or of a different kind.

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REFERENCES

1. Wu, Jin, V. 1992. Dynamic ion-ion and water-ion interactions. *Ion Channels.* 61:1316–1331.

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