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ORIGINAL PAPER

Synchronization of Na/K pump molecules by a train of squared pulses

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Abstract We experimentally studied the Na/K pump currents evoked by a train of squared pulses whose pulse-duration is about the time course of Na-extrusion at physiological conditions. The magnitude of the measured pump current can be as much as three-fold of that induced by the traditional single pulse measurement. The increase in the pump current is directly dependent on the number of pre-pulses. The larger the number of the pre-pulses is, the higher the current magnitude can be obtained. At a particular number of pre-pulses, the pump current becomes saturated. These results suggest that a large number of pre-pulses may synchronize the pump molecules to work at the same pace. As a result, the pump molecules may extrude Na ions at the same time corresponding to the stimulation pulses, and pump in K ions at the same time during the pulse intervals. Therefore, the measured pump current is three-fold of that measured by a single pulse where the outward and inward pump currents are canceled by each other.

Keywords Na/K pump · Synchronization · Oscillating electric field · Manipulation

Introduction

In many living systems, a large amount of ATP molecules are used by Na/K ATPases and other pump molecules to maintain ionic concentration gradients between cytoplasm and extracellular fluids. The generatedelectrochemical potential across the cell membrane is critical to many cell functions, including controlling cell volume, generating electric signals and providing energy for other transporters.

Because of involving ionic movement, many of these pump molecules are sensitive to the membrane potential. Voltage-dependence of the Na/K pump molecules has been widely studied from nerve cells (Rakowski et al., 1989), oocyte (Rakowski et al., 1991), cardiac muscles (Nakao and Gadsby, 1989; Gadsby and Nakao, 1989) and skeletal muscle fibers (Chen and Wu, 2002) showing a sigmoid shaped *I–V* curve. The *I–V* curve exhibits a shallow slope and saturation behavior (Lauger and Apell, 1986; De Weer et al., 1988a; Rakowski et al., 1997). These results indicate that the pump molecules are not particularly sensitive to the membrane potential, and the pump current has an upper limit. Therefore, any fluctuation in the membrane resting potential may require a long period of work for the pump molecules to reinstate it. This system works well in normal physiological conditions. However, during some inordinate conditions, such as cardiac diseases, wound healing, and electrical injury, the membrane resting potential can not be effectively maintained at the physiological value, and consequently, the membrane potential depolarization becomes a common symptom.

Many works have been done to apply an oscillating electrical field in order to active the pump functions. The pioneering work by Tsong and Tissies (Teissie and Tsong, 1980; Serpersu and Tsong, 1983) studied Rb accumulation in red blood cells, and found that a weak oscillating electric field can activate the Na/K ATPase in erythrocytes. Blank and Soo (Blank and Soo, 1989, 1990) have reported that an AC current can either stimulate or inhibit ATP hydrolysis activity of enzymes, depending on the Na/K ratio. A rigorous theory obtained by resolving differential equations

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based on an enzyme reaction loop interacting with a week sinusoidal electric field has predicted the existence of optimal frequency windows, in which an electric field can increase the enzyme reaction rate (Tsong and Astumian, 1986, 1987; Markin et al., 1992; Robertson and Astumian, 1991). Later, a random-telegraph fluctuating (RTF) electric field consisting of alternating square electric pulses with random lifetimes (Xie et al., 1994) and a Gaussian-RTF electric field have been used to activate the Na/K pumps (Xie et al., 1997). A Brownian motion model (Astumian, 1997; Tsong, 2002) and a recent adiabatic pump model (Astumian, 2003) have been further postulated to explain the underlying mechanism.

Recently, we analyzed the underlying mechanisms involved in the low voltage-dependence of the Na/K pump molecules (Chen, 2005). The low sensitivity to the membrane potential is mainly due to the opposite ion-transports, Na-extrusion and K-pumping in, and therefore, their inverse voltage dependence. Any membrane potential change, either depolarization or hyperpolarization, can only facilitate one transport but hinder another, and consequently, can not significantly increase the pump rate. Based on this result, we further considered using an oscillating electric field whose frequency is comparable to the pump's turnover rate to alternatively facilitate both limbs of Na and K transport, and found that the pump rate can be significantly increased (Chen, 2006).

Based on these studies, we developed a synchronization modulation technique to electrically activate the Na/K pump molecules. Our experimental results showed that by this technique, the turnover rate of Na/K pump molecules can be controlled, and can be significantly increased for many folds. In this technique, the first step is to entrain individual pumps to work in the same pace, or synchronization of the pump molecules.

The Na/K pumps are different from ion channels most of which are in a closed state at the membrane resting potential. Because the pump's equilibrium potential, at about -300 mV, is far below the membrane resting potential (Laugher and Apell, 1986; De Weer et al., 1988b) the pump molecules remain pump Na and K ions at all over the physiological membrane potentials. In general, pump molecules work at random pumping pace, and their pump rate follows a statistical distribution based on thermodynamics. In this paper, we present our experimental results in study of pump molecules' synchronization, the first step in electrical activation of the pumps. We studied the Na/K pump currents from skeletal muscle fibers in response to a train of squared pulses whose pulse-duration is comparable to the time-course of Na-extrusion, or the pulse frequency comparable to the pumps' turnover rate at physiological condition. The results show that the pump molecules can be synchronized by a well designed oscillating electric field.

Method and cell preparation

Experimental techniques follow those developed by Hille and Campbell (Hille and Campbell, 1976) and have been used in several labs and ours to study intramembrane charge movement currents (Kovacs et al., 1983; Irving et al., 1987; Hui and Chen, 1992; Chen, 2004a, 2004b). Single skeletal muscle fibers were hand dissected from twitch muscles, semitendonosus of Rana Pippiens frogs, and mounted into a custom-made chamber. The fibers were electrically and ionically separated by two Vaseline partitions into three segments, end pool one, the central pool and end pool two. The dimensions of the partitions and the central pool are 100 μm and 300 μm, respectively. The segments at the two end pools were treated with 0.01% saponin for two minutes and washed out. A voltage clamp (Dagan TEV 2000) was connected to the three pools through Ag/AgCl pellets in order to hold the membrane potential and to monitor the transmembrane currents. We have used this technique to successfully measure the Na/K pump currents in skeletal muscle fibers and to study their voltage dependence (Chen and Wu, 2002). The shape of the measured pump's current-voltage (*I–V*) curve is similar to that from cardiac cells (Gadsby et al., 1985; Gadsby and Nakao, 1989; Rokowski et al., 1997).

The compositions of internal and external solutions follows the recipes used in ours and other labs in study of Na/K pump currents. We also followed Gadsby' work (Gadsby et al., 1985) and adjusted the concentrations of Na and K ions in the external and internal solutions in order to increase the pump currents. The solution compositions are as following:

Internal solution (mM): Na-glutamate, 40; K-glutamate, 22.5; $MgSO_4$, 6.8; Cs_2-EGTA, 20; Cs_2-PIPES, 5; $Tris_2$-Cretinephosphate, 5 and Na_2-ATP, 5.5.

External solution (mM): TEA-Cl, 87.5; NaCl, 15; KCl, 5.4, Na_2HPO_4, 2.15; NaH_2PO_4, 0.85; $CaCl_2$, 1.8; $RbCl_2$, 1.5; $BaCl_2$, 1.5; 3.4 DAP, 3.5, and 1 μM TTX.

External solution with ouabain: the same composition as above but with 1 mM ouabain, a specific inhibitor of the Na/K pumps molecules.

Protocols for electrical stimulation

The membrane was held at the membrane resting potential of -90 mV. Two groups of stimulation protocols were used in our experiments. The first one consisted of only a single stimulation pulse of 30 ms, 90 mV changing the membrane potential to 0 mV, as shown in the upper panel of Fig. 1. We called this Stimulation P1. This kind of single pulse has been used in many labs to study the Na/K pump currents (Rakowski et al., 1989; Gadsby and Nakao, 1989; Rakowski et al., 1997; and Chen and Wu, 2002). The second group

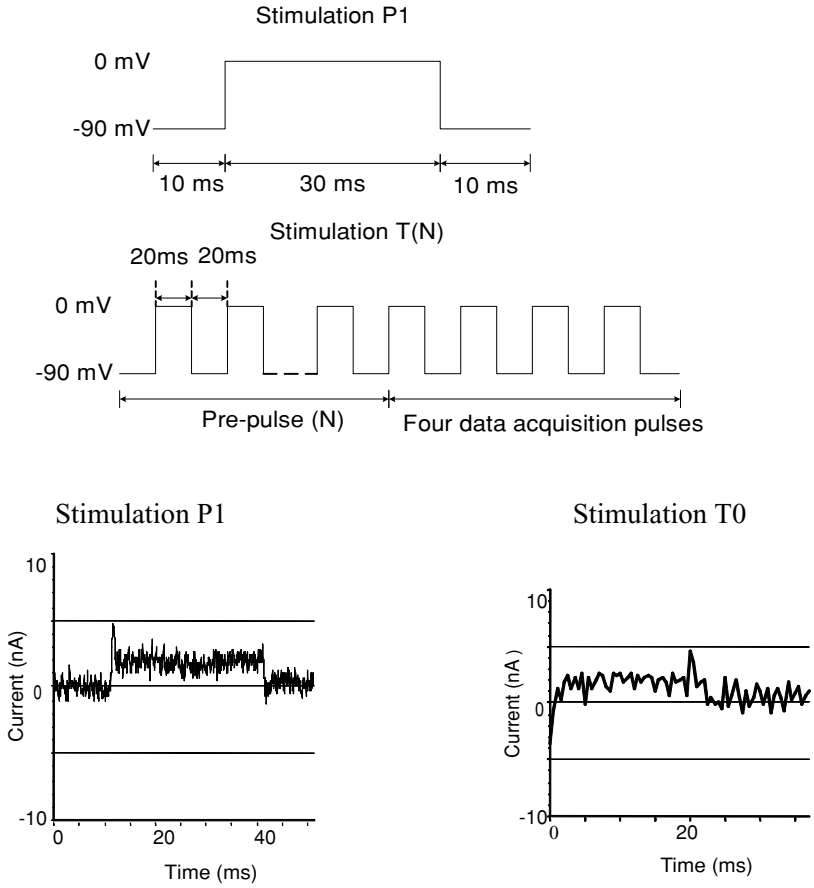

Fig. 1 Two kinds of stimulation protocols. The upper panel shows a single stimulation pulse usually used to measure the pump currents. The middle panel shows a stimulation pulse-train. It starts from a number (N) of pre-pulses followed by four data acquisition pulses. For the pulse-train, only the currents responding to the last four data acquisition pulses were recorded. Na/K pump currents elicited by the single long pulse, P1, and by the pulse-train, T0, are shown as the left and right traces in the lower panel, respectively. Because of many pulse involved, the data acquisition rate for T0 is lower than that for P1

consists of several stimulation protocols. Each stimulation protocol consists of a train of squared pulses. Each pulse has duration of 20 ms and again, a magnitude of 90 mV. The equivalent pulse frequency of 25 Hz is in the range of the physiological turnover rates of the Na/K pumps (De Weer et al., 1988a,b; Lauger 1991). Only the currents evoked by the last four pulses were recorded, which we called data acquisition pulses. The different stimulation protocols only differ in the number (N) of pre-pulses prior to the four data acquisition pulses. The middle panel in Fig. 1 shows the stimulation protocols, T (N). Stimulations T0, T100, T200, T400 and T600 have zero ($N = 0$), 100 ($N = 100$), 200 ($N = 200$), 400 ($N = 400$), and 600 ($N = 600$) pre-pulses, respectively.

The procedure used to identify the Na/K pump current is typical used in many labs including ours. Ion channels were maximally blocked by different channel blockers, including TTX, TEA, Co, Cs and 3, 4-DAP. The stimulation protocols were sequentially delivered to the cell membrane by the voltage clamp and the evoked transmembrane currents were simultaneously recorded. The sequence is always Stimulation P1 first, and then Stimulations T0, T100, T200, T400 and T600, if necessary. After that, the external solution was changed to the same solution with ouabain. Then, the same sequence of stimulation protocols was reapplied to the cell membrane. The P/4 method was used for all of stimulation protocols to subtract linear currents in order to get protein-related non-linear currents. The Na/K pump currents were then defined as ouabain-sensitive currents, which can be obtained by subtracting the pulse-induced non-linear currents in the presence of ouabain from those in the absence of ouabain.

Experimental results

The lower panel of Fig. 1 shows the ouabain-sensitive currents, or the Na/K pump currents responding to Stimulations P1 and T0, respectively. The T0-induced currents were an average for four data acquisition pulses. The two current traces have a similar magnitude, which can be obtained by averaging the last 30 points in the current traces. The pump current responding to the four data acquisition pulses of Stimulation T0 is 2.3 nA, which is qualitatively consistent to that of 1.9 nA, elicited by a single 30 ms pulse of Stimulation P1. This result shows that the pulse-train protocol can be used to measure the pump currents, and the result is consistent with that using the traditional single long pulse.

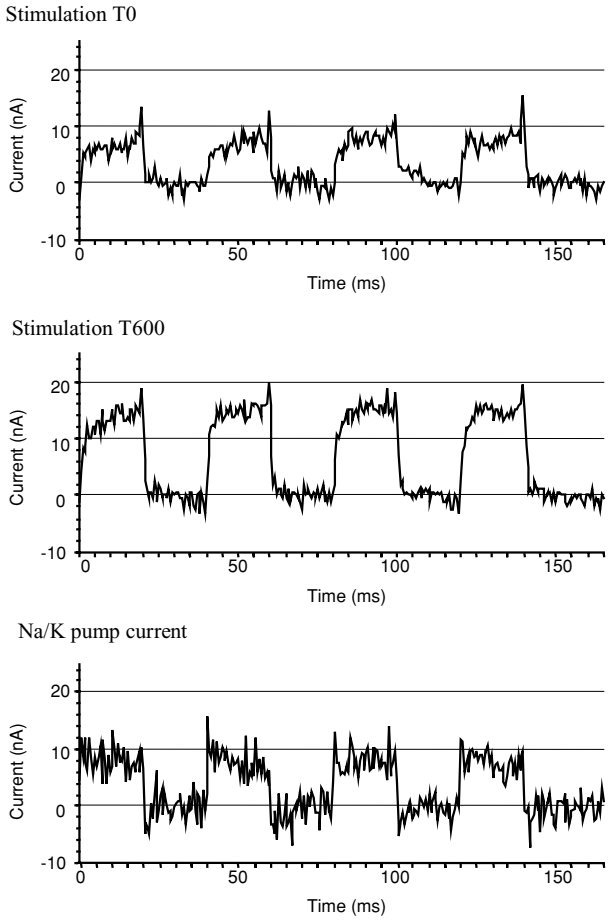

Fig. 2 Upper panel: current evoked by Stimulation protocol T0, Middle panel: current evoked by Stimulation T600. Both are recorded in the absence of ouabain. By subtracting the corresponding currents in the presence of ouabain (not shown) we can get pump currents evoked by T0 and T600, respectively. The T600-induced pump currents are shown in the lower panel, and that induced by T0 has been shown in Fig. 1

The upper trace in Fig. 2 represents the non-linear current evoked by the four data acquisition pulses of Stimulation T0 without pre-pulses in the absence of ouabain. Since the linear currents have been subtracted, these currents were the membrane protein-related non-linear currents including the Na/K pump currents. Similarly, the middle trace represents those currents responding to Stimulation T600, where 600 pre-pulses were prior to the four data acquisition pulses, again in the absence of ouabain. Clearly, the Stimulation T600 evoked nonlinear currents are larger than those elicited by Stimulation T0. The currents evoked by these stimulations in the presence of ouabain were also recorded. The results are not shown here, but as expected, the two current traces were very similar regardless of adding the 600 pre-pulses. By subtracting the corresponding currents in the presence of ouabain from those in the absence of ouabain (upper and middle traces), respectively, we obtained the pump currents evoked by Stimulations T0 and T600. The T0-induced pump currents were averaged for the four pulses, and the result has been shown in Fig. 1 having a magnitude of 2.3 nA. The Stimulation T600-induced pump currents are shown in the lower trace in Fig. 2, where the magnitude of pump currents is about 7.1 nA, about three times increase. Since using the same data acquisition pulses, we can conclude that the 600 pre-pulses made the pump currents increase about three times.

Our working hypothesis is that the pre-pulses alternating the membrane potential for 600 times may synchronize the pump pace of individual pumps to the pulse frequency. Because the pulse frequency is comparable to the turnover rate of the pump molecules, and the pulse duration is similar to the time course of Na-transport (De Weer et al., 1988a,b; Lauger, 1991) at physiological condition, the pulse-train can treat individual pump molecules distinguishably based on their pump phases with respective to its own. If the turnover rates are a little lower than the pulse frequency, the pulse-train may accelerate the pumps, and if they are a little higher than pulse frequency, the pulse-train may slow down the pumps until they reach the pulse frequency. Therefore, the pulse-train may gradually influence those pump molecules individually until they transport Na ions at the same time during the pulses, and leave the K-transport to the pulse intervals. When the pumps work randomly, the inward and outward pump currents cancels resulting in a small net outward pump current. When the pumps are synchronized, the transports of Na-extrusion and the K-pumping in are separated in time. As a result, the magnitude of the pump currents can be increased due to without cancellation.

If it is a phenomenon of synchronization of the pump molecules, it can not be a transient event. It should take time for the pulse-train to synchronize the randomly distributed pump molecules. The larger the number of the pulses is applied to the cell membrane, the more the pump molecules can be synchronized and therefore, the larger the measured pump currents. As long as most of the pump molecules are synchronized the magnitude of the measured pump currents should stop to increase. To prove this hypothesis, we sequentially applied Stimulations T0, T100, T200, T400 and T600 to the cell membrane in the absence of ouabain, and the evoked nonlinear currents including the pump currents are shown as trace A, B, C, D and E in Fig. 3, respectively. The currents were gradually increased with the number of pre-pulses.

In order to obtain the pump currents as a function of the number of pre-pulses, we subtracted Stimulation T0-induced current, trace A, from the corresponding current traces B, C, D and E, evoked by Stimulations T100, T200, T400 and T600, respectively. By this way, other nonlinear currents, and the pump currents induced by T0 were subtracted. The results represent the pure increase in the pump currents due to the increase in the number of pre-pulses. From Fig. 1, the T0-induced pump current of is 2.3 nA. Then, we can plot

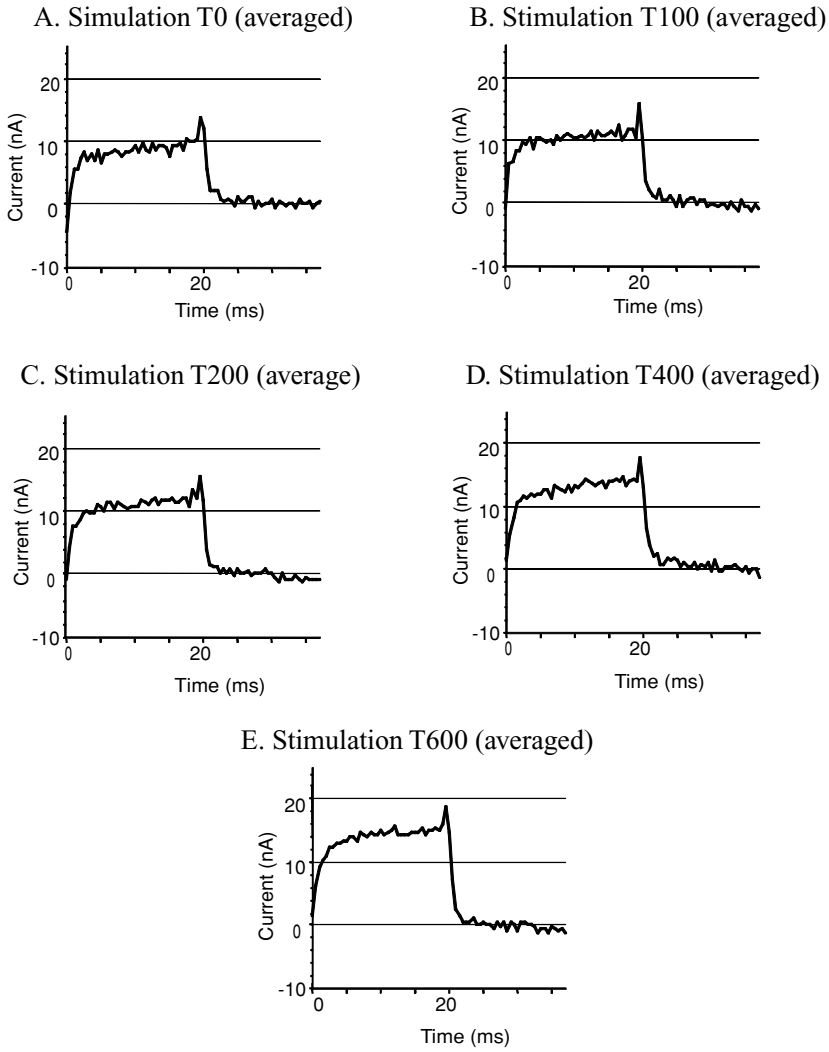

Fig. 3 Trace A, B, C, D and E represents the nonlinear current elicited by Stimulations T0, T100, T200, T400 and T600, respectively. They are averaged currents for four data acquisition pulses

the pump currents as a function of the number of pre-pulses shown in Fig. 4.

It is clear that the pump current elicited by T0 without any pre-pulses has the smallest value. When the pre-pulses were added, the magnitude of the pump currents increased. The more the pre-pulses are applied, the higher the pump current could be measured. This is consistent with our hypothesis that synchronization is a procedure but not a transient event. In addition, seven experiments have been conducted, the results consistently showed a saturation behavior indicating that the measured pump current reached a maximal value and no longer increase even more pre-pulse were applied.

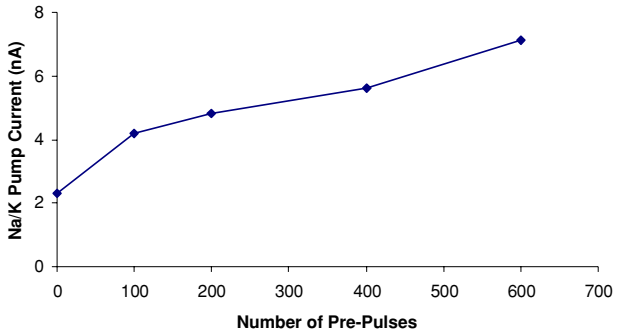

Fig. 4 Pump current increments as a function of different number of pre-pulses

The number of pre-pulses needed to synchronize the pump molecules differs slightly from fiber to fiber. It may be due to different numbers of pump molecules involved in the study because of differences in fiber diameter and pump density. The absolute value at the plateau may differ also. However, the ratios of the resultant maximal pump currents over those elicited by T0 are always smaller than, but close to 3.

Discussion and conclusion

In our experiments, we have carefully identified the pulse-train induced increase in the pump currents. First, all of the ion channel currents were maximally blocked. Secondly, the continuous stimulation-pulse-induced changes in the holding

currents were minimized. In all our experiments, after 600 pre-pulses stimulation, if the membrane holding currents increased over 1 nA which is less than 5% of the holding current, the fiber was given up. In addition, by subtracting the currents in the presence of ouabain from those without ouabain in the same condition allowed us to eliminate all other factors who may affect our measurements. Most importantly, in all of our experiments with ouabain, the pre-pulse-train induced effects were fully eliminated.

As a result, the changes in the pump currents are mainly due to the presence of pre-pulse train. The characteristics of the changes in the pump currents include: (i) the measured outward pump currents are gradually increased with the number of the pre-pulses. (ii) The pump currents finally reach a maximal value. And (iii) The ratio of this maximal value over the pump current measured without pre-pulses is close to 3, a stoichiometric number of the Na/K pump (extruding three Na ions out of the cell in each cycle). These results indicate that the pump molecules can be synchronized by the pre-pulse train with the pulse-duration comparable to the Na-extrusion time course, or the pulse-frequency comparable to the pumps' turnover rate.

This can be discussed as follows: Due to extrusion of three Na ions and pumping in of two K ions, each pump molecule transports net one ion out of the cell in each cycle. If there are N pump molecules in the study with random turnover phases, the Na-extrusion and K-pumping in can not be distinguished. Only a total of net N charges are pumped out per cycle resulting in a unidirectional outward current. When the pump molecules are synchronized, N pumps extrude a total of $3N$ Na ions out of the cells at the same time resulting in an outward pump currents during the stimulation pulses, and leave $2N$ of K ions pumping-in to the pulse intervals. Therefore, the magnitude of the outward pump currents of the synchronized pump molecules should be three times as that of the unsynchronized pump molecules. As long as most of the pump molecules are synchronized, the measured pump currents should become saturated and no longer increase even more pulse are applied.

As the question of what pump currents we measured are, potassium or sodium. We believe they are sodium currents. The reasons include: (i) its outward direction consistent to the direction of the Na-extrusion. (ii) This outward current occurred during the pulses that depolarize the membrane potential that facilitate the Na-extrusion transport but hinder the K-pumping in. And (iii) the consistently showed, close to *three* times increase in the current magnitude from the unsynchronized pump currents, which is consistent to the stoichiometric number. In deed, in this study, we are unable to prove this interpretation. More work needs be done. However, we can predict that if an oscillating, pulsed, AC electric field is applied to the cell membrane with a frequency comparable to the pump rates, the synchronized pump currents should show both outward and inward components in response to the positive and negative pulses, representing the Na-extrusion and K-pumping in. The magnitude ratio of the outward current over the inward currents should be close to 3:2, the stoichoimetric ratio of the Na/K pump currents.

We would like to compare our results with those obtained from other labs. Pioneer works by Apell (Apell and Bersch, 1987) and Gadsby et al. (1989) interrupted the pumping loop by depriving potassium ions and eliminating ATP molecules. The Na/K pumps were restricted to sodium translocation steps. Either by ATP-release or electric pulse, the pump molecules started to move at the same time and then, stopped at the same step. The measured transient pump currents showed relaxation time courses. Those experimental conditions are different from ours. In our experiments, pump molecules continuously run the loop without being interrupted. It is worthwhile to point out that the synchronization we claimed here is the pump loops synchronization instead of pump steps synchronization. Based on the recent results by Gadsby et al. (Holmgren et al., 2000), the time courses for the three distinct and sequential steps in release of Na ions are from μs to a very few ms. Among these steps, the slow charge translocation in both the forwards and backwards directions are nearly electroneutral. Therefore, the Na translocation current is a transient current the time course of that is much shorter than our pulse-duration. In other words, we are able to synchronize the pump loops so that the Na translocation steps of individual pumps are limited during the stimulation pulses, but we can not determine the detailed location of each pump current in the pulse. They may be randomly distributed during the pulse. As a result, the relaxation time courses should not be observed.

As the augment of the difference between our results with the previous works using sinusoidal electric field, random telegram fluctuating pulses or Gaussian RTF electric pulses to activate Na/K pump and other membrane ATP ases, the involved mechanisms are different. All of these studies are based on a concept from an elegant theory of resonance or optimal frequency windows in which an electric field can increase the enzyme reaction rate (Tsong and Astumian, 1986, 1987; Markin et al., 1992; Robertson and Astumian, 1991). Even though in the theory, detailed information of these optimal frequency windows, such as the number, location and bandwidth, was not specified, the previous studies have consistently used optimal frequencies in kilo-Hz (Tsong and Astumian, 1987; Xie, 1994, 1997) and mega-Hz (Robertson and Astumian, 1991) ranges. It is well known that the stoichiometric numbers of the Na/K pumps remain constants in a wide range of the membrane potentials. Therefore, it is unlikely that the pumping loop have been synchronized to such high frequencies. Otherwise, the pump turnover rate will increase from physiological 50 Hz to

kilo-Hz or mega-Hz resulting in an extremely huger increase in the pump currents. The involved mechanisms underlying those activations may be that the pumps are able to absorb energy from these high frequency oscillating electric fields.

In our studies, we used a pulse-train having a very low frequency of about 50 Hz which is comparable to the pumps' physiological turnover rate. It is necessary to point out the results presented in this paper have not dealt with any pump activation. The close to three-fold increase in the measured pump currents does not mean more Na and K ions pumped across the cell membrane. Instead, it only indicates an entrainment or organization of the pump molecules so that the pumping loops are synchronized with applied pulse-train. Indeed, we have further activated the pump functions using a special designed oscillating electric field where the frequency is dynamically changed instead of using a fix frequency in the optimal frequency windows. Results will be reported separately.

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