Interpretation of Action Potential Generation Mechanism in Cells by Potassium Channel "Origami Windmill" Model

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Abstract

The mechanism of cell action potential was explained by using the principle of potassium channel "origami windmill" model. It is inferred that ion channels should include at least two categories: One kind of channel is "special ion channel", its structure is like an origami windmill model. All cations passing through this channel rotate into the interior from one-way, only in and no out. Compared with K^+, they have two states of "open" and "closed", When they are "open", their aperture is not less than K^+ diameter. When "closed", their aperture is smaller than K^+ diameter, but not smaller than Na^+ diameter. The other channel is the "universal ion channel". All Ions passing through this channel unidirectional flow too, only out and no in. Compared with K^+, they have two states of "open" and "closed", When they are "open", their aperture is not less than K^+ diameter. When "closed", their aperture is smaller than K^+ diameter, but not smaller than Na^+ diameter. This model reasonably explains the whole process of action potential occurrence, and supports Hodgkin, Huxley 's experimental the results of action potential. This model does not support their explanation of the mechanism of action potential generation in cells and the core ideas of "membrane theory" and "ion theory". It negates the selective filter atomic model and the propeller model established by MacKinnon et al. It is tiped that the main role of "sodium-potassium pump" or "ATPase" is not responsible for the transport of Na^+ and K^+ from the inside and outside of the cell and maintaining cell membrane potential. The channels through which ions enter and escape cells are independent. This suggests that most channels may be sharing in the same direction by other inorganic ions and organic molecules.

Key words: Potassium channel; Origami windmill; Model; Resting potential; Action potential; Sodium-potassium pump

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The establishment of potassium ion channel "origami windmill" model[1] has gone through the deduction process of practice-theory-practice-re-theory. Since 1994, the authors have invented a series of rehabilitation treatment equipment for encephalopathy using transcranial electrical stimulation and transcranial magnetic electrical stimulation technology, such as Brain Function Rehabilitation Therapy Instrument[2,3], Parkinson's Disease Therapy Instrument[4], Alzheimer's Disease Therapy Instrument[5,6], Depression Therapy Instrument[7], etc. They has been widely used in clinical practice of Parkinson's disease, Alzheimer's disease and other major brain neurological diseases, and the rehabilitation effect is remarkable.

In order to elucidate the mechanism of instrumental therapy and the etiology of Major Brain Neurological Diseases, the author, as an inventor, applied the principles of physical biology to trace the origin of encephalopathy, and successively proposed "The theory of brain cell activation" [8] and "The theory of dove-like particles"[9] both at the cellular molecular level. During this period, the research work naturally involved action potential, ion channels, ion transport process, neurotransmitters and other basic issues related to life science. The research result found that applying the existing theoretical model of potassium channel, the explanation of some basic problems in life science is not reasonable, such as mechanism of action potential generation[10-13] 、 function of sodium-potassium pump[14,15] and other problems. Their explanations are far-fetched.

Based on the above facts, and MacKinnon Laboratory's actual observation of the channel crystal structure[16], combining the research of action potential of Alan Hodgkin and Andrew Huxley[10,12], the model of potassium channel "origami windmill" has been deduced. In this paper, the mechanism of action potential (AP) in cells is explained by using the model principle.

Basic principles

Model Principle of "Origami Windmill" : K^+ and the positively charged amino acids in pore helixes form a repulsive force, which pushes the "blade" back and makes the "windmill" rotate. The aperture size of K^+ channel varies with the speed of windmill. This determines the "opening" and "closing" of channel holes. Its characteristic is that four pore helixes to form an independent functional unit, synchronized unidirectional rotation. They rotate clockwise or counterclockwise,but one windmill of a passage can only rotate in one direction. It transports K^+ passively and unilaterally and has no dependence on ATP.

There should be at least two major types of channels on the neuron membrane corresponding to the entry and exit of K^+, Na^+. Among them, one kind of channel is K^+ channel, which we call "special ion channel". Its structure is like an origami windmill model. All cations passing through this channel rotate into the interior from one-way, only in and no out. Compared with K^+, they have two states of "open" and "closed", when they are "open", their aperture is not less than K^+ diameter (2.33 Å) [16], it can rotate cations including K^+ in extracellular fluid into cells. When "closed", their aperture is smaller than K^+ diameter, but not smaller than Na^+ diameter (1.90 Å) [16]. This kind of channels respond to the stimulus of an external electromagnetic field. Correspondingly, there should be another kind of channel, Na^+ channel. We call it "universal ion channel". All Ions passing through this channel unidirectional flow too, only out and no in. Compared with K^+, they have two states of "open" and "closed", When they are "open", their aperture is not less than K^+ diameter. When "closed", their aperture is smaller than K^+ diameter, but not smaller than Na^+ diameter.

According to the different diameters of K^+, Na^+, in a straight line. The ratio of the number of K^+, Na^+ permutations with the same linear length to each other is about 2:3. That is to say, the linear length of two K^+ is approximately equal to the linear length of three Na^+. Although this is only a rough estimate. In the latter analysis, The ratio of 2:3 is enough to reflect the importance of different diameter of K^+ and Na^+ in the process of action potential generation. So let's assume that only 300 NaCL molecules can be accommodated on the inner surface of cell membrane, if 200 K^+ rotates from outside the cell into the cell, correspondingly, 300 Na^+ ions are extruded from the cells. there will be 100 excess negative charges（CL^-）in the cell. That is, 2 K^+ rotate into the cell、Extrude 3 Na^+, Excess 1 negative charge (CL^-), proportion 2:3:1; Let's assume that Assuming that only 200 KCL molecules can be accommodated on the inner surface of cell membrane, if 200 K^+ rotates from inside the cell out the cell, correspondingly, 300 Na^+ ions vacant locations are left in the cell. When 300 Na^+ were rotated from extracellular to intracellular to replenish K^+ position, there will be 100 excess positive charges（Na^+）in the cell. That is, 3 Na^+ rotate into the cell、release 2 K^+, Excess 1 positive charge (Na^+), proportion 3:2:1; CL^- and Na^+ represent negatively charged anions and positively charged cations on the inner surface of cell membranes, respectively. Anions and cations are not limited to CL^- and Na^+.

Action potential and resting potential

Hodgkin and Huxley recorded action potentials for the first time in cells (Figure A、Figure B). We use the K^+ channel "origami windmill" model principle to explain their measured results. The threshold of exciting action potential is -45mV. At the instant of action potential generation, the "universal ion channel" is "open" to K^+. The windmill's rotational speed increase occurs in the rising phase, that is, from slow to fast. The intracellular K^+ run out of the cell from the "universal ion channel". Extracellular Na^+ is rotated into the cell to replenish the K^+ position. That is, Na^+ rotate into the cell、release K^+, Excess positive charge (Na^+), proportion 3:2:1. At 40mV, the "universal ion channel" is "closed" relative to K^+. This process is rising phase, which is a depolarization process. From -45mV to 40mV, they are all led by the Na^+ which rotated into the cell. The polarity of membrane potential was reversed completely, from "inside negative and outside positive" to "inside positive and outside negative", this process takes 1 ms .
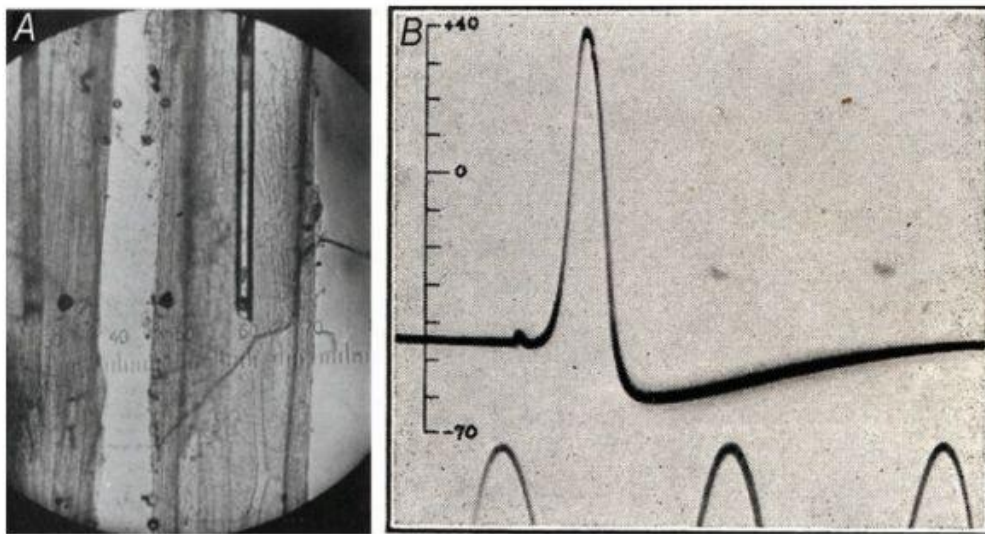
Intracellular recording of the squid giant axon action potential[10]

Figure A, photomicrograph of an electrode inside a squid giant axon (diameter～500 μm). Two views of the same axon are visible from an ingenious system of mirrors devised by Huxley. This allowed simultaneous viewing of the electrode from both front and side and was essential to avoid the electrode damaging the nerve membrane as it was threaded down the axon. Figure B, the first intracellular recording of an action potential.

The highest point of rising phase is 40mV, this is also the "inflection point" of the falling phase. The "special ion channel" is "open" to K^+, "Windmill" rotation deceleration occurs in the falling phase, that is, from fast to slow. Extracellular K^+ is rotated into the cell to occupy the Na^+ position, Na^+ was squeezed out of the cell through "universal ion channel". That is, K^+ which be

rotated into the cell、Na^+ which be extruded , excess negative charge (CL^-), proportion 2:3:1; At the lowest point -65mV, The "special ion channel" is "close" to K^+. This process is the falling phase, which is the process of repolarization. From 40mV to -65mV, they are all led by the K^+ which rotated into the cell. The polarity of membrane potential returned to resting state, from "inside positive and outside negative" to "inside negative and outside positive", this process takes 1 ms . Membrane potential can be directly reduced from 40mV to -65mV, over -40mV, the falling phase is more than the rising phase by "25mV". The reason for this asymmetry is that K^+ diameter is larger than Na^+ diameter.

The lowest point is -65mV, which is commonly known as resting membrane potential. Hodgkin and Huxley used the Hodgkin-Huxley model to calculate the membrane potential of giant axon cells of squid, it is found that the calculated results are in good agreement with the measured results of real experiments. At this membrane potential, the intracellular K^+ concentration was higher than that of extracellular K^+ concentration, extracellular Na^+ concentration was higher than intracellular Na^+ concentration. The so-called resting states (-65 mV to -45mV) are also relative. At this time, the windmill is still spinning at a low speed. The attraction between Na^+ which rotated into the cell and the negative charge (CL^-) on the inner surface of the cell, and the restraint by the gradient diffusion force of Na^+ concentration inside and outside the cell, redundant Na^+ is trapped on the inner surface of the cell membrane. When depolarization occurs, that leads to the expansion of cell membranes, the pore size of the "universal ion channel" is extended. The cell membrane is elastic. "Universal ion Channel" should be "Force Sensitive Ion Channel". It responds to membrane tension. This expansion process, are led by the Na^+ which flow into the cell. The expansive force of the cell membrane can also be called the "repulsive volume force". It changes the intracellular dynamics. It is neither van der Waals force nor related to charge-independent. It has a threshold, according to the principle of mechanical-electrical coupling of cell membrane, the corresponding threshold of membrane potential is "-45mV".

It is also found from Figure B that, a "small peak value" appeared before the action potential occurred. This is because there is a small abnormal fluctuation in the speed of the windmill. The "excess" Na^+ which be rotated into cells instantaneously inflows and instantaneously outflows, this leads to a small "rising phase" and "falling phase" in the resting membrane potential instantaneously. It can also be seen as a "omen" of action potential.

The action potential, whether rising phase or falling phase, did not leave any mark at the 0mV potential point. This is because the area replacement ratio of K^+ and Na^+ on the inner surface of cell membrane is unreasonable when the proportion of positive and negative charges in cell is balanced. That is to say, at the 0 mV potential point, on the inner surface of cell membrane, when the action potential rises, there is positions of K^+ that can be supplemented by Na^+, when the action potential falls the replacement of Na^+ by K^+ has not been completed. Similarly, at the highest (40mV) and lowest (-65mV) of membrane potential, the area replacement ratio of K^+ and Na^+ on the inner surface of cell membrane is reasonable. That is to say, the ions on the inner surface of the cell membrane have been saturated, but the cell membrane has not yet expanded. At this moment, the number of positive and negative charges is unbalanced. The surface area of the inner membrane of a single cell is fixed, and beyond this area, it will cause expansion!

Yuh-Nung Jan, Lily Yeh Jan, Yifan Cheng and others have analyzed NOMPC of Drosophila melanogaster by single-particle cryoelectronic microscopy. They confirmed that NOMPC responds to the movement of cytoskeleton, that to expand the channels in cell membranes, allowing ions to quickly pass through the channels into cells and generate electrical currents[17]. In other words, The action potential is due to the expansion of the pore size of the "universal ion channel" by the mechanical expansion force of the cell membrane.

That K^+ inward flow causes action potential to fall phase, however, it is not excluded that other cations can also participate in it; That Na^+ inward flow causes action potential to rise phase, the same is true. Na^+ has the highest probability of activating action potential. However, the possibility of other cations stimulating action potentials cannot be ruled out. For example, K^+ may also trigger action potentials before the special ion channels are "closed".

Sodium-Potassium Pump and Selective Filter

The hypothesis of "sodium-potassium pump" was proposed by R.B. Dean，it is based on Julius Bernstein's membrane theory and Hodgkin's and Katz's ion theory. The core viewpoints of membrane theory and ion theory are as follows: The formation of "Negative inside and positive outside" resting potential of cell membrane is due to that the corresponding negative charge remained in the cell after K^+ outflow. So Dean believed that the cells transported K^+, Na^+, in reverse concentration and there must be a "pump" on the cell membrane. Hodgkin explained the formation of resting potentials by quoting Dean's hypothesis, and thus speculated that: The sodium-potassium pump consumes ATP, that inhibiting ATP activity will inhibit sodium outflow.

Jens C. Skou found that ATPase activity depended on the co-participation of Na^+ and K^+ and making experiments confirmed that ouabain could inhibit ATPase activity. Because of the coupling between ATPase activity and Na^+, K^+, it was believed that ATPase is mainly involved in the formation of resting potential [14,15]. After that, some hypotheses such as calcium ion pump and hydrogen potassium ion pump were put forward successively.

The point of view in this paper is just the opposite, think: The formation of "Negative inside and positive outside" resting potential of cell membrane is due to K^+ influx. It is speculated that the so-called "sodium-potassium pump" or "ATPase" is not responsible for the transport of Na^+, K^+ Intracellular and extracellular, and the maintenance of cell membrane potential. ATPase activity depends on the common parameters of Na^+ and K^+ ions and ouabain inhibits ATPase activity. This connection is not enough to suggest that ATPase must be a "pump". From a chemical point of view, so-called sodium-potassium pump, from the combination of Na^+ and pump to the release of K^+ into cells, it takes 10ms and six steps [18]. It can be said that it is impossible to complete a large number of Na^+, K^+ internal and external transshipment tasks in a short time. That the 2:3 ratio of K^+ to Na^+ and the precise coupling all occur on the same "transporter" is also too idealistic to be realistic.

In addition, MacKinnon Laboratory's Atomic Model of Selective Filter shows that when the Selective Filter is in an open state, K^+ channel rejects Na^+ which smaller than K^+ [16]. This explanation is too far-fetched. The facts may be the same as those described in the "origami windmill" model. The selection of ions is determined by the change of pore size of special ion channels. It's not as complicated as think.

Rotation speed estimation of "Origami Windmill"

In theory, the K^+ permeability of a K^+ channel is 10^8 in 1s. The actual results are as follows: only change of K^+ concentration by one in ten million is needed to cause a great change in membrane potential, equivalent to 400000 K^+/times. Within one action potential duration (about 2 ms), assuming that a single neuron has 2000 K^+ channels, the result is 200 K^+/channel [9]. The frequency range of human normal brain waves is 1～30Hz, which can be divided into four bands:δ wave (1～3Hz), θ wave (4～7Hz), α wave (8～13Hz), and β wave (14～30Hz). Among them，α wave (8～13Hz), this is the basic rhythm of normal human brain waves, averaging 10 Hz [19], corresponding that a single time course is 100 ms. Assuming that the windmill can spin

100 K^{+} into the cell every time it rotates, corresponding to 10Hz, the average speed of the windmill is 20 r/s; 1～30Hz, corresponding to 2～60r/s. This estimate is very close to the speed of the molecular motor measured in the laboratory. 8 r/s and 100 r/s [1,20]. Actions over 1000Hz, whether linear swing or rotation, or switching between "on" and "off", have a too high frequency. Nieng Yan believes that the rotational speed of glucose transporters in somatic cells is 1200 r/s, in the brain is 6000 r/s, and the best model of transporters is the "revolving door". It is inappropriate to disseminate these to the public through authoritative media in the form of popular science. Just as Yigong Shi reveals the fine three-dimensional structure of the gamma-secretase complex based on the Aβ hypothesis, this does not prove that he has caught the culprit of Alzheimer's disease (AD). Their work is not closely related to major diseases such as AD, diabetes, heart disease and even cancer [21-26].

Conclusion

The K^{+} channel "origami windmill" model supports the experimental results of Hodgkin and Huxley's action potential. It does not support their interpretation of mechanism of action potential generation in cells and the core viewpoints of "membrane theory" and "ion theory". It negates the selective filter atomic model and the propeller model established by MacKinnon et al. The principle of the origami windmill model tips the main role of "sodium-potassium pump" or "ATPase" is not responsible for the transport of Na^{+} and K^{+} from the inside and outside of the cell and maintaining cell membrane potential, that discovered by Jens C. Skou. The channels through which ions enter and escape cells are independent. The number of these two types of channels will not be too large. Most channels may be sharing in the same direction by other inorganic ions and organic molecules; Perhaps there are no "pumps" or "motors" in cells at all. Xiaowei Zhuang detected of DNA rotation at millisecond time resolution is a remarkable breakthrough[27]. But whether DNA rotation depends on Motors should be questioned. Therefore, this model is not confined to the transport of Na^{+}, K^{+}, but may also assume the function of "carrier protein", such as glucose-Na^{+} transports in the same direction, glucose is rotated into the cells along with a lot of Na^{+}. If Cu^{2+} and other heavy metal cations are rotated into cells and occupy K^{+} position on the inner surface of cell membrane, it will lead to abnormal apoptosis of brain cells when reducing membrane potential. The relationship between the cytochrome C[28] which discovered by Xiaodong Wang and the abnormal apoptosis deserves further study.

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