# “Driving force”-dependent block in the inward rectifier K+ channel

Ion channels are protein pores allowing specific ions to pass through cell membrane to maintain resting membrane potential, or to generate various physiological electrical signals. The inward rectifier $K^+$ channel (Kir channel) is noted for the strong inward rectification, which means the $K^+$ ions flow much more easily in the inward direction than in the outward direction (Fig.1).

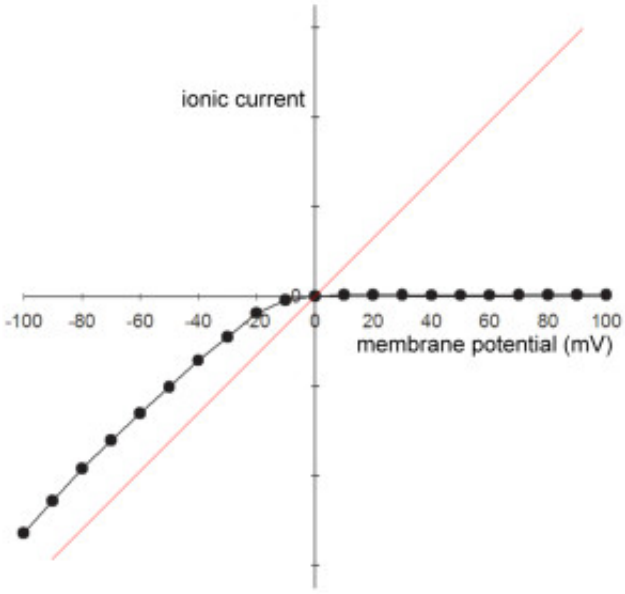


Fig. 1. Current-voltage relationships of inward rectifier K+ channels in symmetric K+ concentrations (reversal potential = 0 mV) in the presence of intracellular blockers. The outward K+ current is blocked, and the inward current is scarcely affected. Note that at voltages near but negative to the reversal potential, the inward current can be still inhibited due to flux-dependent block, because unidirectional outward flux is inevitable near the equilibrium at the molecular level, although the net flux is inward.

This fascinating phenomenon had been observed in starfish eggs in 1976, later in the human heart and nerve cells, and also in the cloned Kir channels after the 1990s in the molecular era. Physiologists have known that the inward rectification can be observed when the positively charged blockers, such as $Mg^{2+}$ and polyamines, are present in the intracellular solutions. However, the molecular scenario underlying the rectification remains as an interesting topic. Researchers from Taiwan proposed a novel biophysical mechanism based on their delicate experiments on the cloned Kir2.1 channel, published in the journal *Biophysical Chemistry*. They demonstrated that the steep changes in the apparent affinity of the blockage near the reversal potential (the voltage at

which the net $K^+$ current is zero and changes its direction) actually result from the flux-coupling effect by the conducting $K^+$ ion on the blocker along the narrow long pore. This study may represent an advance in understanding of how the nanoscale Kir channel pore utilizes the thermodynamic “driving force” to regulate electrical signal.

The driving force for ion conduction across the channels is a collective tendency resulting from both the concentration difference and the electrical voltage difference across the cell membrane. Macroscopically, diffusion is the net transport of small particles, such as $K^+$ ions, from the area of high to low concentration. Microscopically, each ion is randomly pushed by the surrounding water molecules due to thermal motion, and just jiggles independently without a specific direction. In the presence of the voltage difference across the membrane, the diffusion of the positively charged $K^+$ ions is counteracted by the electrical forces; the process is called electrodiffusion. The direction of the net ion flux is determined by the driving force, which is the difference of the membrane voltage from the reversal potential. The driving force for electrodiffusion is equivalent to the electrochemical potential difference across the membrane.

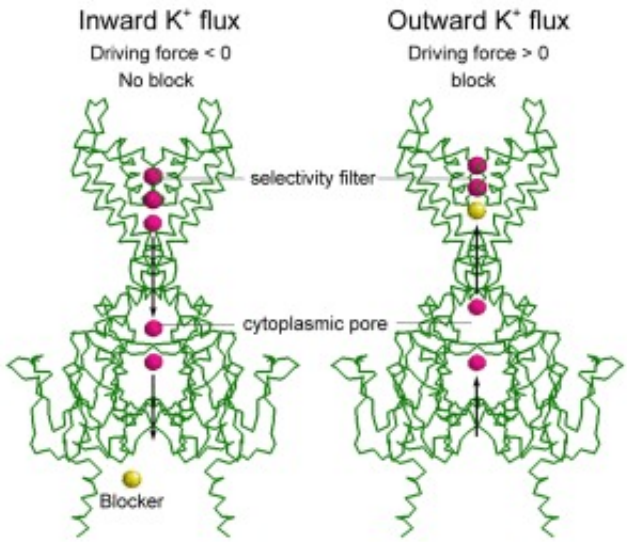


Fig. 2. The Kir2.1 channel has a single-file, multi-ion cytoplasmic pore. When the driving force for K+ ion conduction is negative, the inward K+ flux precludes the blocker from encountering the deeper binding site. When the driving force favors outward conduction, the blocker can be coupled by the outward K+ flux, and reach the binding site to occlude the K+ current

Why does the Kir channel have strong inward rectification while other $K^+$ channels lack this feature? The key to answer this question lies in the structure-function relationship of this channel. Previous X-ray structural studies have revealed that the Kir2.1 channel has a narrow long cytoplasmic pore structure, which extends the single-file $K^+$ ion pathway more than 30 Å beyond the 12 Å length evolutionary reserved selectivity filter. Several $K^+$ ions can reside simultaneously

along the cytoplasmic pore in the Kir2.1 channel. The diffusion or electrodiffusion in this narrow long pore is special because the movement between ions is not independent. The flux-coupling effect can occur in a single-file, multi-ion pore, which means the ions cannot pass over each other and have to line up and move concertedly.

As Dr. Chi-Pan Hsieh and colleagues propose in their paper, when the driving force is negative, the predominantly inward $K^+$ ion flux exert the coupling effect on the intracellular blocking ion, and prevent the blocker to bind onto the deeper binding site within the channel pore. When the driving force favors outward conduction, the blocker can be coupled by the outward $K^+$ flux, and reach the binding site to occlude the $K^+$ current (Fig.2). As a result, inward rectification can be recorded in the current-voltage curve in Kir channels in the voltage-clamp study. More interestingly, the authors show that the “driving force”-dependence block, and thus the flux-dependent inward rectification, can be demonstrated even in the presence of the concentration gradient alone, when there is no voltage difference across the membrane.

Thus, the “thermodynamic driving force” can exert real directional impact on the ion movement in the single-file, multi-ion pore. The entropic tendency for electrodiffusion in the nanoscale channel can be harnessed for regulating physiological signals. In this regard, the physical mechanism underlying the rectification of Kir channels is reminiscent of the rectifier in the electrical circuit and in Feynman’s imaginary Brownian ratchet.

***Chi-Pan Hsieh***
*Department of Medical Education, Far Eastern Memorial Hospital, Taiwan*

## Publication

Driving force-dependent block by internal Ba(2+) on the Kir2.1 channel: Mechanistic insight into inward rectification.
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