The inconstancy of the human heart

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The improper timing of the human heartbeat can now be connected to the arcana of potassium channel gating. What is more, it turns out that a bizarre kind of ion-channel behaviour is in fact quite conformist.

MOST of us take for granted the smooth, regular flow of blood through our veins. But as anyone knows who has experienced an irregular heartbeat (cardiac arrhythmia) or witnessed the catastrophic effects of ventricular fibrillation in a heart attack, the steady lub-dub of the human heart beats perilously close to an abyss of aperiodicity.

The elaborate collection of ion channels in cardiac cell membranes has been designed by evolution to generate a periodic electrical wave and also to preserve its stability in the face of glitches of all kinds — random voltage fluctuations, invasion of electric currents from elsewhere in the cardiac circuitry, and environmental challenges such as drugs and natural toxins. On page 833 of this issue[1], Smith *et al.* describe the molecular mechanism by which one of these cardiac ion channels — HERG by name — acts to protect the heart against inappropriate rhythmicity. In their examination of HERG, they also resolve an irritating headscratcher of a problem concerning the structure and function of these 'upside-down' K^+ channels.

A newcomer to the molecular galaxy of K^+ channels[2], HERG was recently identified as the culprit in a genetically determined cardiac arrhythmia[3]. People lacking a functional HERG gene display an abnormality on their electrocardiogram called 'long Q–T syndrome', which, while causing no distress in itself, predisposes them to sudden cardiac arrest.

HERG's amino-acid sequence places it squarely in the familiar, extensively studied class of voltage-gated K^+ (VGK) channels (see box). Typical VGK channels open rapidly (in a few milliseconds) in response to a positive-going (depolarizing) voltage pulse, and then, upon continued application of this voltage, turn off on a slower timescale. This turning-off process, termed inactivation, is observed in all known VGK channels and results from a conformational change that occurs after the channel has been opened by depolarization.

But, surprisingly, HERG does not behave in this way. Very little K^+ current is elicited by a positive voltage pulse, but if after such a pulse the membrane voltage is brought back to very negative values, large inward K^+ currents grow over a few milliseconds (Fig. 1). Thus, in comparison to other VGK channels, HERG is functionally upside-down.

A possible explanation for this contrary behaviour[4] could be that HERG is mechanistically a conventional VGK channel, but that the rates of the activation and inactivation processes are reversed, so that activation is slow (tens of milliseconds), whereas inactivation and recovery from inactivation are, say, tenfold faster.

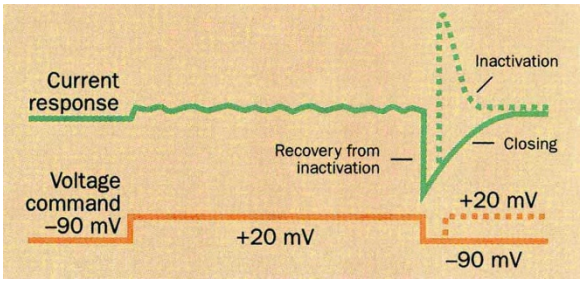
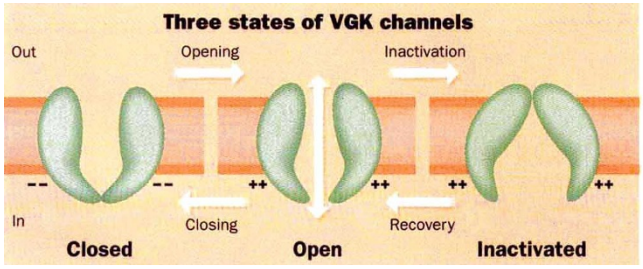
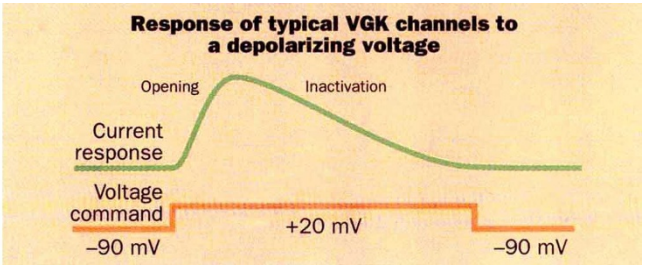


FIG. 1 HERG gating responses. With HERG channels, little K^+ current flows during a long depolarizing pulse. However, a subsequent negative-going pulse leads to rapid removal of inactivation, and a large inward K^+ current is seen; if the voltage is quickly returned to a positive value (dashed curves), a large current flows outwards.

A positive voltage would then cause channels to open slowly, but as soon as one opens, it would inactivate. Thus, very few conducting channels would appear at a sustained positive voltage. If the membrane potential were then shifted negative, a fast recovery from inactivation

Voltage-gated K^+ channels





VOLTAGE-GATED potassium (VGK) channels are found in nerve, muscle and other types of electrically interesting cells. All VGK channels can exist in three basic conformations: closed, open and inactivated, of which only the open conformation can conduct K^+ ions. (A few VGK channels can also exist in an 'N-inactivated' state different from that depicted here.) These conformations are voltage-dependent: negative voltage drives the reactions leftwards towards the closed state, and positive voltage favours the open and inactivated states. Conventional VGK channels are often studied by holding the membrane at a highly negative voltage, where all channels are closed, and then applying a positive-going, or depolarizing voltage pulse. As channels open over several milliseconds in response to the test pulse, outward K^+ current rises, but then after a longer time (tens to thousands of milliseconds, depending on the particular channel), inactivation sets in, and the K^+ currents fall. The detailed shape of the K^+ current time course reflects the balance between the forward rates, opening and inactivation, and the backward rates, closing and recovery from inactivation. C. M.