Commentary
Gap Junction Voltage Dependence: A Clear Picture Emerges

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All vertebrate gap junction channels display voltage-dependent gating. Historically, voltage-dependent behaviors have been characterized as being transjunctional voltage (Vj) and membrane voltage (Vm) dependent. The transjunctional voltage dependence of gap junction channels composed of two identical hemichannels, each composed of identical connexins subunits (a homotypic channel) is usually symmetric and is often referred as Vj-dependent gating. Vj steps of equal amplitude but opposite polarity will result in junctional currents that are mirror images of each other in terms of magnitude and kinetics (Harris et al., 1981; Spray et al., 1981). Figure 1 in Oh et al. (2000) illustrates such symmetric (slow) Vj dependence, as well as the characteristic steady state “residual” junctional conductance.

It is interesting to note that the first demonstration of voltage dependence in cell-to-cell communication is best considered to be a subset of Vj dependence. It is the rectifying or asymmetric voltage dependence first observed in the crayfish rectifying synapse by Fursphan and Potter (1959), where the kinetics are quite rapid, which gave rise to the term fast Vj dependence. Similar rapid asymmetric effects of voltage on junctional conductance have been described in vertebrate gap junctions as well. It is usually observed in heterotypic gap junction channels. Heterotypic channels are composed of two hemichannels of different connexin composition. The hemichannel of one cell can be composed of Cx32, for example, while the adjacent cell contributes a hemichannel composed of Cx26. Many such combinations of connexins produce rectifying or asymmetric Vj dependence. This fast Vj dependence is thought to be embodied in the rectification of single channel conductance (Bukauskas et al., 1995). That is, single channel conductance of heterotypic gap junction channels is dependent on Vj and its polarity. Gap junction channels composed of hemichannels that contain more than one type of connexin are called heteromeric forms and display a variety of behaviors intermediate between those of homotypic and heterotypic forms (He et al., 1999; Brink et al., 1997).

At the single-channel level, two types of gating that can account for the behavior of macroscopic junctional conductance are typically observed. At the single-channel level, the term Vj gating refers to rapid transitions between a fully open state and a subconductance state. A second form of gating in hemichannels has been provisionally termed loop gating and is characterized by a series of step-like transitions between the open and closed states with a time course of many milliseconds (Trexler et al., 1996). Rather than closing to a stable subconductance state, closure follows a series of step-wise transitions declining to a truly nonconductive state. (see Figure 2 in Trexler et al., 1996, and Figure 7 in Oh et al., 2000) The term loop gating was coined because of the resemblance of these stepwise gating transitions to those ascribed to hemichannel docking by Bukauskas and Weingart (1994), which presumably involves interactions between the extracellular loop domains of connexins. Both of these gating motifs can be observed in multichannel records of gap junction channels using dual whole-cell patch clamp (Bukauskas and Weingart, 1994). But the dual whole-cell method, while innovative, has a number of technical limitations. Paramount among them is a poor signal-to-noise ratio and an even poorer time resolution due to the introduction of whole-cell capacitance.

One last development in understanding the evolution of the gap junction channel gating story is that Paul et al. (1991) showed that Cx46 was able to function as a hemichannel or half-gap junction channel. Single oocytes injected with mRNA for Cx46 displayed large outward membrane currents at inside positive voltages. In both the attached and the excised patch mode, it is possible to observe single channels whose behavior mimics the macroscopic phenomena, as subsequently demonstrated by Trexler et al. (1996). Unfortunately, however, not all connexins appear to readily gate under the same conditions that make Cx46 hemichannels gate in single cells or when undocked or unapposed.

With this background, let us turn to Oh et al. (2000), in this issue of The Journal. First, the authors have used a Cx32Cx43 chimera, originally constructed by Pfahnl et al.(1997), that forms functional hemichannels. The rationale for using this construct is based in the observation made in oocytes pairs by Versells et al. (1994) that the second amino acid of the NH₂ terminus was a determinant of gating polarity. The authors therefore constructed a variant of the Cx32Cx43E1chimera in which the second amino acid, which is normally neu-
gating mechanisms, Vj gating and loop gating, are more, mutations that affect the polarity of Vj gating do not affect loop gating, providing evidence that the two gating mechanisms, Vj gating and loop gating, are molecularly distinct.

The article by Oh et al. (2000) is one in a series by this group of investigators that uses sound biophysical methods of analysis and site-directed mutagenesis to demonstrate the nature of connexin gating. It bridges the gap between macroscopic description and underlying molecular mechanism, and articulates a cleaner picture of the intricacies of voltage-dependent gating in gap junction channels.

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