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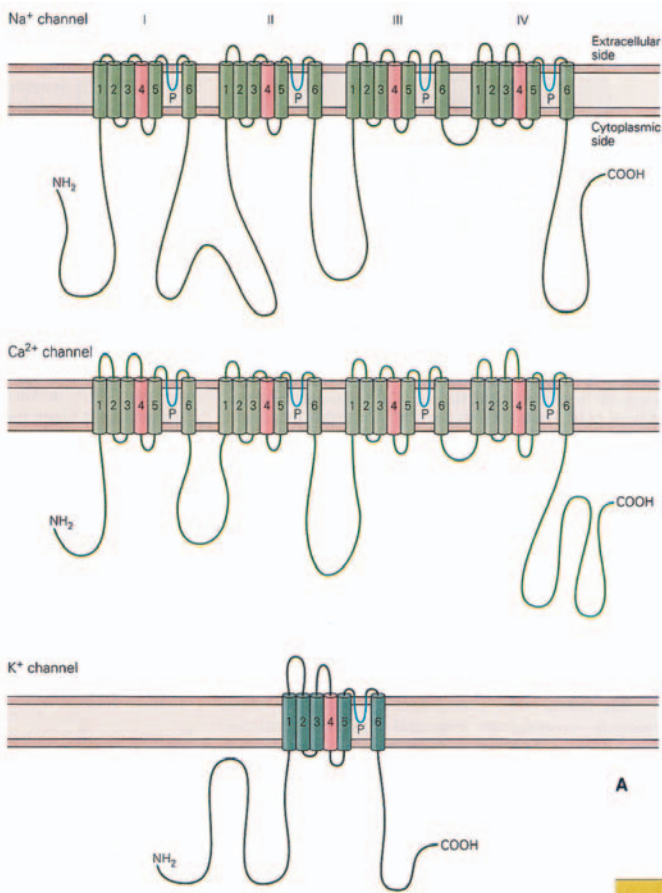


Figure 9.14 The pore-forming subunits of the voltage-gated Na^+ , Ca^{2+} , and K^+ channels are composed of a common repeated domain. The α -subunit of the Na^+ and Ca^{2+} channels consists of a single polypeptide chain with four repeats (I-IV) of a domain that contains six membrane-spanning α -helical regions (S1-S6). A stretch of amino acids, the P region between α -helices 5 and 6, forms a loop that dips into and out of the membrane. The S4 segment is shown in red, representing its net positive charge. The fourfold repetition of the P region is believed to form a major part of the pore lining (see Figure 9-15). The K^+ channel, in contrast, has only a single repeat of the six α -helices and the P region. Four K^+ channel subunits are assembled to form a complete channel (see Figure 6-12). (Adapted from Catterall 1988, Stevens 1991.)

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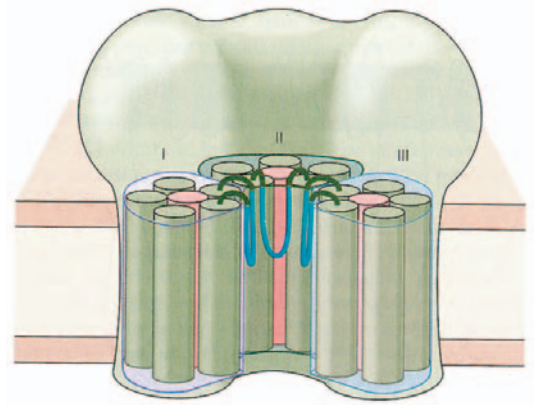


Figure 9-15 The four membrane-spanning domains of the α -subunit in voltage-gated Na^+ and Ca^{2+} channels form the channel pore. The tertiary structure of the channels proposed here is based on the secondary structures shown in Figure 9-14. The central pore is surrounded by the four internally repeated domains (M-1 to M-IV). (Only three of the domains are shown here for clarity.) Each quadrant of the channel includes six cylinders, which represent six putative membrane-spanning α -helices. The S4 segment (in red) is thought to be involved in gating because it contains a significant net charge. The protruding loop in each quadrant represents the P region segment that dips into the membrane to form the most narrow region of the wall of the pore.

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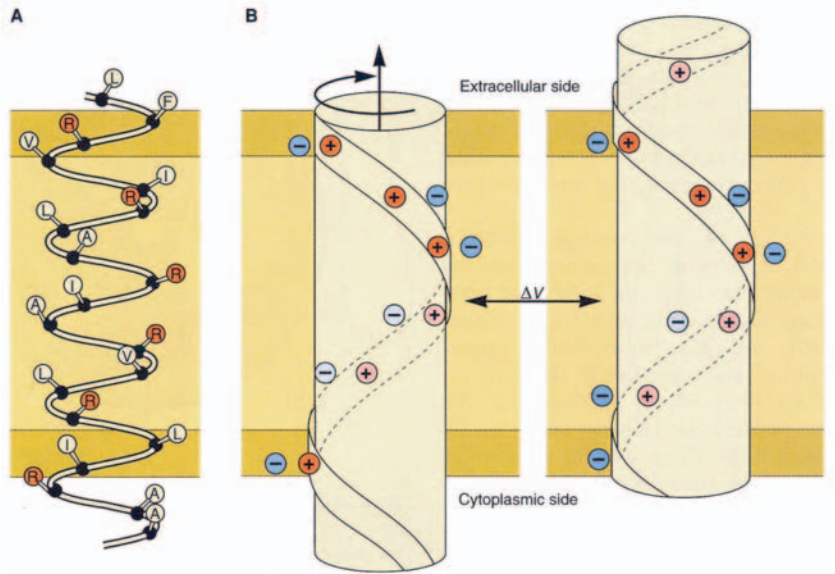


Fig. 6.13. Catterall's sliding helix model of gating charge movement in the sodium channel. Segment S4 is presumed to form an α -helix crossing the membrane as shown on the left. Here the black circles represent the α -carbon atoms of the different amino acid residues and the open circles represent their side chains. Residues are indicated by the single letter code, with R showing the positively charged arginine; the rest are non-polar. The arginine residues thus form a helix of positive charges, shown on the right. The model proposes that these form ion pairs with an array of negative charges on other segments, and that depolarization allows an outward movement of the S4 segment by one step along this array. (From Catterall, 1986a.)

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| | Shaker gating charges? | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|----------------------|------------------------|---|---|---|----------------|---|---|---|---|---|---------------|---|---|---|---|----------------|---|----------------|---|---|---|---|---|---|----------------|---|---|---|---|---|---|---|---|---|---|
| | Outside to S3 | | | | | | | | | | Outside to S5 | | | | | | | | | | | | | | | | | | | | | | | | |
| Shaker | L | A | I | L | R | V | I | R | L | V | R | V | F | R | I | F | K | L ⁺ | S | R | H | S | K | G | L ⁺ | Q | | | | | | | | | |
| Na (I) | V | S | A | L | R | T | F | R | V | L | R | A | L | K | T | I | S | V | I | P | G | L | K | T | I | V | | | | | | | | | |
| Ca (I) | V | K | A | L | R | A | F | R | V | L | R | P | L | R | L | V | S | G | V | P | S | L | Q | V | V | L | | | | | | | | | |
| Na (II) | G ⁺ | L | S | V | L | R | S | F | R | L | L | R | V | F | K | L ⁺ | A | K | S | W | P | T | L | N | M | L | I | | | | | | | | |
| Ca (II) | I | S | V | L | R | C | I | R | L | L | R | L | F | K | I | T | K | Y | W | T | S | L | S | N | L | V | | | | | | | | | |
| Na (III) | L | G | A | I | K | S | L | R | T | L | R | A | L | R | P | L | R | A | L | S | R | F | E | G | M | R | | | | | | | | | |
| Ca (III) | I | S | V | V | K | I | L | R | V | L | R | V | L | R | P | L | R | A | I | N | R | A | K | G | L | K | | | | | | | | | |
| Na (IV) | P | T | L | F | R ⁺ | V | I | R | L | A | R | I | G | R | I | L | R | L | I | K | G | A | K | G | I | R | | | | | | | | | |
| Ca (IV) | E | S | A | R | I | S | S | A | F | F | R | L | F | R | V | M | R | L | I | K | L | L | S | R | A | E | | | | | | | | | |
| I_h | Y | K | T | A | R | A | L | R | I | V | R | F | T | K | I | L | S | L | L | R | L | L | R | L | S | R | L | I | R | L | I | R | Y | I | H |
| CNG | Y | P | E | I | R | L | N | R | L | L | R | I | S | R | M | F | E | F | F | Q | R | T | E | T | R | T | | | | | | | | | |

19.3 Homologous Sequences of S4 Segments Comparison of amino acid sequences of S4 regions of the Shaker K channel, $\text{Na}_v 1.2$ Na channel, $\text{Ca}_v 1.1$ Ca channel, HCN1 I_h channel, and CNG1 CNG channel. The four homologous repeat domains are shown for Na and Ca channels. Basic arginine (R) and lysine (K) residues are highlighted.