



**FIGURE 13.7** Overview of the membrane topology of voltage-gated ion channel  $\alpha$ -subunits. (a) The voltage-sensing S4 transmembrane segments (*green*) contain several positively charged amino acid residues and the segments that constitute the ion channel pore (*shown in red*) are the S5, S6, and pore loop segments. (b) Membrane topology of auxiliary subunits of  $\text{Na}_v$ ,  $\text{Ca}_v$ , and  $\text{K}_v$  ion channels. (From Catterall, W.A. et al., *Toxicon*, 49, 124, 2007.)

contraction and for regulation of the heart rate, so dihydropyridines are used for treatment of hypertension and cardiac arrhythmia.  $\text{Ca}_v3.1$  and  $\text{Ca}_v3.2$  subunits are found in the sino-atrial nodes where they play important roles for cardiac pacemaking.

Release of neurotransmitters from synaptic nerve terminals is triggered by influx of  $\text{Ca}^{2+}$  ions via  $\text{Ca}_v2.1$  (P/Q-type) or  $\text{Ca}_v2.2$  (N-type) subunits which are expressed in all nerve terminals. When neuronal APs travel down the axon and reach the nerve terminal, they provide the depolarization necessary for activation of  $\text{Ca}_v$ s leading to  $\text{Ca}^{2+}$  influx. The  $\text{Ca}_v2.1$  and  $\text{Ca}_v2.2$  subunits bind directly to proteins of the protein machinery involved in membrane fusion of neurotransmitter-containing vesicles.

A similar role of  $\text{Ca}_v$ s is found in various endocrine cells such as the pancreatic  $\beta$ -cells in which ATP-mediated closing of  $\text{K}_{\text{ATP}}$  channels leads to cellular depolarization, activation of  $\text{Ca}_v1.3$  channels, and release of insulin-containing vesicles (Figure 13.5).

### 13.3.3 PHARMACOLOGY OF VOLTAGE-GATED CALCIUM CHANNELS

There are two types of inhibition of  $\text{Ca}_v$  function, namely, blockade of the ion channel pore and allosteric modulation of ion channel function. An example of pore blockade is cadmium ( $\text{Cd}^{2+}$ ) which produces nonselective inhibition of all type of  $\text{Ca}_v$ s. The mechanism behind this effect is that