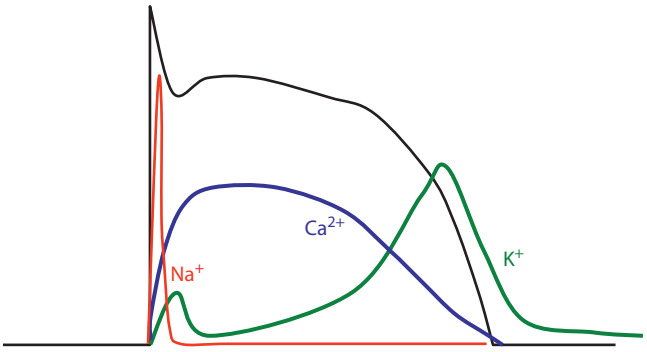


**FIGURE 13.1** Cardiac action potential (curve in black) and time-course of selective $Na^+$, $Ca^{2+}$, and $K^+$ currents.

membrane potential, respectively. The net ion movement across the membrane is zero once the two forces equal each other which happens at the so-called equilibrium potential. This potential is determined by the ion distribution across the membrane, and for the typical intracellular and extracellular ion concentrations the equilibrium potentials are shown in Table 13.1.

The effects on the membrane potential of activation of selective ion channels are shown in Figure 13.1. The cardiac action potential (AP) is initialized by opening of voltage-gated $Na^+$ channels, and the influx of the positively charged $Na^+$ ions leads to a fast positive shift in the membrane potential (depolarization). Subsequently, voltage-gated $Ca^{2+}$ channels are opened and the influx of $Ca^{2+}$ ions keeps the membrane potential depolarized. Fast $K^+$ channels are activated early in the response and attenuate the depolarization, but the key role of the $K^+$ currents is to terminate the AP after about 350 ms when numerous $K^+$ channels open and the outflow of the positively charged $K^+$ ions mediate the repolarization.

The consequence of the sequential opening of $Na^+$–$Ca^{2+}$ and $K^+$-selective channels is thus that the cell membrane potential will be pulled in the direction of the equilibrium potential for these ion species, i.e., about +70 mV for $Na^+$, +120 mV for $Ca^{2+}$, and −93 mV for $K^+$ (Table 13.1). Often the cell does not fully reach the equilibrium potential as shown for the cardiac AP, since several types of channels are usually open at the same time. Likewise the impact on the membrane potential of physiological or pharmacological ion channel block or activation depends on the presence of other simultaneous conductances and is not just linearly correlated to the number of ion channels being affected. Thus, it can be complicated to predict the functional effect of modulating ion channel function, and extensive target validation studies have to be conducted to establish the anticipated role of an ion channel subtype in an organ.

### 13.1.3 Gating of Ion Channels

Whereas it was clear to Hodgkin and Huxley that a sequential increase in $Na^+$ and $K^+$ membrane conductances underlies the neuronal AP, their method could not reveal the nature of the conductance pathway. This had to await another technological break through. In 1976, Neher and Sakmann reported the opening and closing of single acetylcholine-gated ion channels in striated muscle using a method by which they electrically isolated a patch of membrane in situ with a glass pipette. The method was called patch–clamp with reference to the patch of tissue and the clamp of the transmembrane voltage used to generate the electrical driving force. Since then the method has been extensively used to describe the characteristics and function of ion channels in all cells. Initially, endogenous currents in cells were measured, but following the cloning area the combination of this functional method and heterologous expression of cloned ion channels has been strong in the target-driven drug discovery process.