barriers. Ultimately, indirect methods must be validated by defining a correlation with patch clamp results, as patch clamp results are the definitive evaluation of a compound's ability to influence ion channel activity.

A basic patch clamp system consists of a micropipette with an opening on the order of 1 μm pressed against the surface of a cell. The inside of the micropipette covers a limited number of ion channels, and a seal with high electrical resistance ("gigaohm seal") is created by suction on the surface of the cell. An electrode, salt solution inside the micropipette, and the appropriate electrical amplification and monitoring systems can then be employed to either maintain a constant voltage while monitoring current or maintain a constant current while monitoring changes in membrane potential in the presence of test compounds.[86] The process itself is time-consuming, labor-intensive, and even well-trained electrophysiologist can characterize only a few compounds per day. Ultimately, this has limited the use of patch clamp methods in high throughput screening programs, but efforts to increase screening throughput have begun to emerge (Figure 4.39).

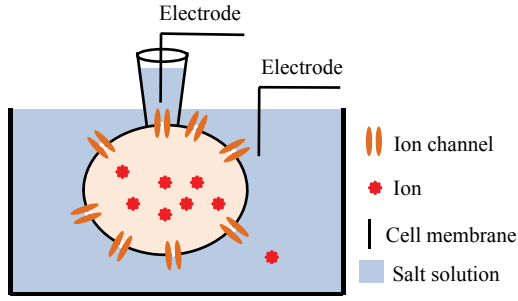

FIGURE 4.39 A basic patch clamp system consists of a micropipette with an opening on the order of 1 μm pressed against the surface of a cell. The inside of the micropipette covers a limited number of ion channels, and a seal with high electrical resistance ("gigaohm seal") is created by suction on the surface of the cell. An electrode, salt solution inside the micropipette, and the appropriate electrical amplification and monitoring systems can then be employed to either maintain a constant voltage while monitoring current or maintain a constant current while monitoring changes in membrane potential in the presence of test compounds.

Plate-based perforated patch clamp technology increased the patch clamp screening capacity when it was introduced along with the IonWorks™ HT platform. In this assay system, a specially designed 384-well plate (referred to as a PatchPlate) configured with a 1–2 μm hole at the bottom of each well allows for the suspension of a single cell over the