contain gates. So, in addition to an inner helix gate, comparable to the one found in voltage-gated ion channels, $K_{ir}3$ has a cytosolic gate, the G loop gate that is important for regulation channel function.

The $K_{ir}6$ channels are expressed both in heart, vasculature, nerve, and in the pancreatic β-cells. This channel subtype can only be expressed in cells when it co-assembles with its accessory subunit, the so-called sulfonyl urea receptors (SUR) of the ABC transporter family. The β-cell subtype is composed of 4 $K_{ir}6.2$ + 4 SUR1. Like other K_{ir} channels it is activated by binding of phosphatidylinositol-4,5-bisphosphate (PIP_2). In contrast, the complex is blocked by ATP binding to the internal surface of $K_{ir}6.2$ and activated by MgADP binding to the nucleotide-binding domains of SUR1. The channel complex is also denoted the K_{ATP} channel and it is interesting for two reasons: it is a key regulatory protein in the β-cells coupling plasma glucose levels to insulin secretion, and the SUR has a well-exploited high-affinity drug binding site.

Briefly, insulin secretion is regulated by the following mechanism: an increase in plasma glucose leads, through an increased ATP level in the β-cells, to block of the K_{ATP} channel, depolarization, Ca^{2+}-influx, and insulin secretion (Figure 13.5). If this regulation is dysfunctional as in many type-2 diabetic patients, a similar functional effect can be obtained by directly blocking the K_{ATP} channel pharmacologically. The drug-binding site on SUR1 is on the inside of TM15 (plus partly on the inside of TM14), and the bulky substitution mutation S1237Y disrupts the site. Tolbutamide binds to this site only, whereas glibenclamide and metiglinide (Figure 13.6) bind to this as well as to a neighboring benzamido site. The latter low-affinity site is shared with the cardiac and vascular subunits SUR2A and SUR2B, respectively.

The cardiovascular side effects of the SUR-blockers are minimal whereas SUR-activators such as cromakalim and diazoxide which have been attempted primarily for the treatment of arterial hypertension, had to be abandoned since they cause orthostatic hypotension and reflex tachycardia.

The K_V channels fall into 12 subfamilies, which are all gated by changes in the membrane potential, but exhibit different kinetics. K_V channels can be composed of four different subunits from the same subfamily giving numerous possibilities for variation. Several K_V channel subfamilies are interesting drug targets. Retigabine is an activator of the $K_V7.2/3$ heteromultimeric channel and was in 2011 approved for the treatment of partial epilepsy, and XE-991 is a memory enhancing compound blocking the same channel (Figure 13.6) used in preclinical research.

Class III anti-arrhythmics block K_V channels in the heart (K_V1, K_V4, K_V11 subtypes) leading to a prolonged cardiac AP and termination of the so-called re-entry arrhythmia. Dofetilide, D-sotalol, and other anti-arrhythmics are selective for the K_V11 channels (hERG channels). These drugs show

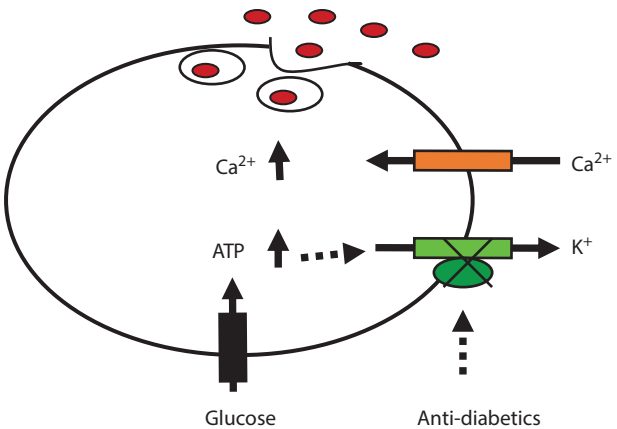

FIGURE 13.5 Ion channels in pancreatic β-cells and insulin secretion. The K channel subtype is called K_{ATP} and it is composed of the two molecular subunits $K_{ir}6.2$ and SUR1.