The K_V11 channel has a high-affinity binding site in the pore, which interacts with drugs of very different classes including antihistamines, antipsychotics, antidepressants, antibiotics, and many more. Pro-arrhythmia caused by drug binding to this site and channel block has been a major reason for withdrawal of drugs from the market and discontinued drug development projects, so the K_V11 channel has become a major cardiac safety pharmacology issue. The Ca^{2+}-activated K^+ channels, K_{Ca}, are divided into three families depending on their single-channel conductance. They are gated by Ca^{2+} binding either directly to the channel or indirectly to a constitutively bound calmodulin. The channels are generally involved in attenuating the activity of a given cell by hyperpolarizing this, when the internal Ca^{2+} concentration rises, thereby functioning as a molecular break.

Transient receptor potential (TRP) cation channels belong structurally to this group having six TM, and cation permeable pore loop between S5 and S6. Despite the structural similarity to K_V channels, the 28 different TRP subtypes can be either selective to Na^+/K^+, Mg^{2+} or Ca^{2+}, and functionally they may associate and be regulated by a number of G-protein-coupled receptors, kinases, and phospholipases. The mammalian TRP channels are divided into six subfamilies: TRPA for ankyrin (TRPA1), TRPC for canonical (TRPC1–7), TRPM for melastatin (TRPM1–8), TRPP for polycystin (TRPP2, TRPP3, TRPP5), TRPML for mucolipin (TRPML1–3), and TRPV for vanilloid (TRPV1–6) and TRPA (TRPA1). Because of the channels' many (patho)physiological roles, including roles in pain, cardiovascular, pulmonary and urinary system, cell proliferation, irritant and thermosensing, they have received a lot of attention from the pharmaceutical industry. Channel modulators could both target the activator ligand binding site, second messenger sites, the pore and possible allosteric sites. The TRP channel that has attracted the most attention as a potential drug target is the TRPV1 channel. This ion channel is activated not only by noxious heat but also by capsaicin, a constituent of chili pepper. TRPV1 has also been found to be up-regulated in various animal models of chronic pain and selective antagonists of TRPV1 reduce pain sensation in these models. Selective antagonists of TRPV1 are currently undergoing clinical trials in patients suffering from different types of chronic pain. Safety data however revealed that TRPV1 inhibition induced a mild increase in body temperature, wherefore the systemic use of TRPV1 inhibitors is currently debated. For now, the only TRP channel modulator on the market is a capsaicin patch (Qutenza) used for pain relief which likely works by inducing a desensitization of TRPV1-bearing nociceptive neurons.

13.3 VOLTAGE-GATED CALCIUM CHANNELS

13.3.1 Structure and Molecular Biology

The discovery of voltage-gated calcium channels (Ca_V) was originally made in the 1950s, through an investigation of crab leg muscle contraction. These experiments revealed that both membrane depolarization and muscle contraction depend on extracellular calcium ions, inferring that the muscle cells possess some membrane molecules enabling calcium to selectively permeate. By use of electrophysiological techniques, it was later found that a variety of functionally distinct Ca_Vs exist and that these ion channels are also expressed in nerve cells.

Functionally, Ca_Vs are closed at the resting membrane potential (i.e., −50 to −80 mV), but are activated by depolarization. Based on this and pharmacological properties, the 10 cloned α-subunits can be grouped in three families: $Ca_V1.x$ (L-type): high-voltage-activated dihydropyridine-sensitive calcium channels, requiring membrane potentials of ca. −20 to +10 mV to activate; $Ca_V2.x$: high-voltage activated dihydropyridine-insensitive channels; (T-type, $Ca_V3.x$): low-voltage activated currents which activate at much more negative membrane potentials, typically −50 to −40 mV. Following activation, Ca_Vs inactivate in the presence of sustained membrane depolarization, although the speed of inactivation can vary from ~50 ms to several seconds. Voltage-activated calcium currents, measured in native tissues, have traditionally been classified as L-, N-, P/Q- or R-type or T-type currents (see Table 13.2).