A. Introduction

Voltage-activated L-type calcium channels regulate the intracellular concentration of calcium and contribute thereby to calcium signaling in numerous cells. These channels are widely distributed in the animal kingdom and are an essential part of many excitatory and non-excitatory mammalian cells. The opening of these channels is primarily regulated by the membrane potential, but is also modulated by a wide variety of hormones, protein kinases, protein phosphatases, toxins, and drugs. Site directed mutagenesis has identified sites on these channels which interact specifically with other proteins, inhibitors, and ions. This chapter will focus on these recent developments. The older findings have been summarized in several excellent reviews (STRIESSNIG et al. 1993; HOFMANN et al. 1994; CATTERALL 1995; DE WAARD et al. 1996a).

B. Subunit Composition and Genes of the Calcium Channel Complex

I. Subunit Composition of L-Type Calcium Channels

Calcium channels are heterooligomeric complexes of five proteins (Fig. 1): (a) the $\alpha_1$ subunit, which contains the binding sites for all known calcium channel blockers, the voltage-sensor, the selectivity filter and the ion-conducting pore; (b) the intracellularly located $\beta$ subunit; (c + d) the $\alpha_2\delta$ subunit, a disulfide linked dimer; and (e) the transmembrane $\gamma$ subunit (HOFMANN et al. 1994).

II. Genes

1. The $\alpha_1$ Subunit

Most of the prominent features of the calcium channel complex can be assigned to the $\alpha_1$ subunit. The $\alpha_1$ subunit contains the ion-conducting pore, the selectivity filter of the pore, the voltage sensor and the interaction sites for the $\beta$ subunits, the $\beta\gamma$ subunits of the G proteins, the $\alpha_2\delta$ subunit, the calcium channel blockers and activators. Nine individual genes have been identified for the $\alpha_1$ subunit, which are homologous to each other and encode proteins of predicted molecular masses of 212–273 kDa. They belong to the same multi-
Fig. 1. Putative structure of the calcium channel complex. Proposed structures of the \( \alpha_1 \) subunit (top) and the accessory \( \beta \), \( \alpha_2\delta \) and \( \gamma \) subunits are indicated. A disulfide bridge (s) connects the transmembrane \( \delta \) and the extracellular \( \alpha_5 \) subunit. The molecular diversity of the \( \alpha_1 \) subunit and pharmacological properties are indicated. \( HVA \), high voltage activated; \( LVA \), low voltage activated.

gene family as voltage-activated sodium and potassium channels and share a common ancestral protein with them. Hydrophobicity analysis of the \( \alpha_1 \) subunits predicts a transmembrane topology with four homologous repeats, each containing five hydrophobic putative \( \alpha \) helices and one amphiphatic segment (Fig. 1).