Chapter 4

The Voltage-Activated, Calcium Antagonist-Sensitive Calcium Channels: Their Structure, Composition and Calcium Antagonist Binding Sites

“A little after this my ink began to fail me, and so I contented myself to use it sparingly.”

DANIEL DEFOE, in “Robinson Crusoe,” 1719.

Robinson Crusoe may have had good reasons for husbanding his supply of ink so carefully, but so far as this monograph is concerned there is a great deal more to write. In particular, before explaining how the cardiovascular system responds to the calcium antagonists and in particular to amlodipine—which is one of the most recent newcomers to the field and which seems to be excitingly different from its predecessors—it is probably useful to summarize what is known about the receptors with which these compounds interact. At the molecular level this means describing the structure and chemistry of the Ca$^{2+}$-conducting channels because it is here that the high affinity “receptors” for these drugs are located.

The Calcium Conducting Channels

As mentioned in the preface of this monograph, the last few years have seen some quite remarkable advances in our understanding of the membrane-located channels which selectively admit Ca$^{2+}$ ions. These channels are formed from proteins which, whilst being an integral part of the membrane, are arranged so as to form ion-selective pores. In this, as in many other respects, the Ca$^{2+}$-conducting channels resemble their Na$^{+}$ and K$^{+}$-conducting counterparts. Under normal circumstances these Ca$^{2+}$ channels specifically and selectively admit Ca$^{2+}$ ions, and are insensitive to agents which interfere with the functioning of the other ion-selective channels (Fleckenstein, 1988).

The Ca$^{2+}$ channels are easily subdivided into two major sub-groups in accordance with their location and primary function. These subtypes are:

(I) the voltage-activated, transsarcolemmal channels which, when activated, facilitate the inward movement of Ca$^{2+}$ ions across the normally impermeable lipid-containing cell membrane; and

(II) the Ca$^{2+}$ release channels of the sarcoplasmic reticulum. These channels facilitate the movement Ca$^{2+}$ ions from storage loci in the sarcoplasmic reticulum, which is an intracellular organelle, into the cytosol (Figure 4.1) where they contribute to the “pool” of Ca$^{2+}$ which activates contraction. In passing it may be of interest to note that it is an un-
controlled activation of these Ca^{2+}-release channels in the sarcoplasmic reticulum which accounts for much of the Ca^{2+}-overloading which occurs during the early moments of ischaemia (see Chapter 11).

It is the first of these channels – that is, the voltage-activated, transsarcolemmal Ca^{2+} channels (or VOC’s – voltage operated Ca^{2+} channels – as they are sometimes known) which is the main topic of this chapter. The choice of these channels for detailed description was certainly not made on an ad hoc basis, because some of them contain the high affinity binding sites for the calcium antagonists.

**The Voltage-Activated Calcium Conducting Channels**

These channels are found in most but not all cells (Bean, 1989). For example, they are not found in platelets, or in red blood cells. When present, however, they are surprisingly heterogeneous, so much so that depending on their biophysical properties (threshold of activation, duration of opening, etc.) and