Abstract Calcium-regulated transcription plays a key role in converting electrical activity at the membrane into long-lasting structural and biochemical changes in excitable cells. Although several calcium influx pathways contribute to the intracellular calcium rise that follows membrane depolarization in neurons, calcium influx through L-type calcium channels (LTCs) and NMDA receptors is particularly effective at activating gene expression. In this chapter, we review some of the experiments implicating LTCs in the induction of gene expression in response to neuronal activity and discuss some of the mechanisms that explain the dependence of activity-induced transcription on LTCs. We will focus our discussion on studies that explore the features of LTCs that allow them to activate the transcription factor CREB, and we will discuss recent studies from our group that identify the C-terminus of the LTC as a protein that regulates transcription directly in the nucleus.

6.1 L-type Calcium Channels

Voltage-gated calcium channels (VGCC) are an important route of calcium entry into neurons and are essential for converting electrical activity into biochemical events in excitable cells (Catterall, Goldin and Waxman 2005). All VGCCs have a common ability to carry calcium in response to depolarization of the membrane but they differ in their subcellular localization, biophysical properties and in their ability to regulate specific biochemical processes. VGCCs are classified into L, N, P/Q, R and T types based on their pharmacological and biophysical properties, and are composed of four protein subunits: a pore forming $\alpha_1$ subunit, and $\beta$, $\alpha_2\delta$ and $\gamma$ subunits that modulate gating and trafficking (Tsien and Tsien 1990). Neuronal L-type channels contain one of three $\alpha_1$ subunits: CaV1.2, CaV1.3 or CaV1.4. CaV1.2 and CaV1.3 form the predominant LTCs in the brain and have been implicated in a wide variety of neuronal functions including promoting survival, increasing dendritic arborization and regulating synaptic plasticity (Galli, Meucci, Scorziello, Werge, Calissano, and Schettini 1995; Moosmang, Haider, Klugbauer, Adelsberger, Langwieser, Muller, Stiess, Marais, Schulla, and Lacinova 2005; Redman, Kashani and Ghosh 2002).
LTCs have a number of features that set them apart from other types of VGCCs. They are blocked by dihydropyridines (DHPs), are activated at relatively depolarized potentials, and have slow rates of activation and inactivation (Tsien and Tsien 1990). LTCs are localized in the cell body, dendrites and postsynaptic membranes of adult neurons, making them ideally poised to control the signal transduction pathways that are activated post-synaptically (Hell, Westenbroek, Warner, Ahlijanian, Prystay, Gilbert, Snutch, and Catterall 1993; Westenbroek, Ahlijanian and Catterall 1990). Finally, LTCs are particularly effective at activating gene expression in response to electrical activity. A key question, however, is what features of LTCs allow them to activate the signaling pathways that lead to the nucleus.

6.2 L-Type Channels, CREB and c-fos

The first indication that LTCs were unusually effective at activating gene expression came from the experiments by Morgan and Curran who reported that depolarizing cells with high potassium provoked an influx of calcium ions via VGCCs that led to the transcription of the immediate-early gene c-fos (Morgan and Curran 1986). Inhibition of LTCs with DHPs blocked the induction of c-fos, suggesting a role for LTCs in regulating the transcription of this gene in response to neuronal activity. Murphy and colleagues then showed that blocking and activating LTCs respectively eliminated and increased basal c-fos expression in spontaneously active neuronal cultures (Murphy, Worley, and Baraban 1991). This implied that LTCs play a role in the induction of c-fos expression in response to endogenous electrical activity. Furthermore, they found that LTCs contributed less than 20% of the synaptically-induced calcium elevation, significantly less than NMDA or kainate receptors, suggesting that the route of calcium entry rather than the absolute amplitude of the calcium rise was important for the activation of c-fos. These early studies showed that calcium influx through LTCs specifically activates signaling pathways that lead to the induction of c-fos transcription.

Dissection of the c-fos promoter by a number of groups identified two main calcium-regulated response elements, the calcium response element (CRE) and the serum response element (SRE) (Miranati, Ginty, Huang, Chatila, and Greenberg 1995; Sheng, Dougan, McFadden, and Greenberg 1988). The CRE binds to the transcription factor CREB and the SRE binds to serum response factor (SRF) both of which are activated by calcium influx in neurons. CREB has emerged as a major regulator of calcium signaling in the brain and has been implicated in neuronal development, survival and plasticity (Lonze and Ginty 2002). Early studies by Sheng and Greenberg first demonstrated that calcium influx through LTCs is particularly effective at activating CREB-dependent transcription (Sheng, McFadden, and Greenberg 1990). Blockers of LTCs potently block the activation of CREB reporter genes, and calcium influx through LTCs in developing cortical neurons is substantially more effective at activating CREB than equivalent calcium elevations through NMDA receptors, suggesting that LTCs are specifically linked to CREB activity (Bading, Ginty, and Greenberg 1993). The most compelling illustration of...