L-Type Calcium Channel Antagonists and Suppression of Expression of Plasminogen Receptors
Is the Missing Link the L-Type Calcium Channel?
Ghassan Bkaily, Danielle Jacques

Several types of voltage-dependent Ca\(^{2+}\) channels were reported in many excitable and nonexcitable cell types, including the L-, T-, P-, N-, and Q-types; the isradipine sensitive steady-state resting R-type; and the nifedipine resistant R-type channels. The presence of some of these voltage-dependent Ca\(^{2+}\) channel types depends on cell origin. Among these channels, the L-type is the most studied channel because of the large number of Ca\(^{2+}\) blockers that affect its function. Historically, calcium channel antagonists were developed before the discovery of the L-type Ca\(^{2+}\) channel. These Ca\(^{2+}\) channel antagonists are divided into 3 classes of drugs: benzoiazepines (such as verapamil), dihydropyridines (such as amlodipine), and phenylalkylamines (such as diltiazem). The 3 classes of L-type Ca\(^{2+}\) channel antagonists have different relative selectivity for cardiac and vascular tissues. Their effects depend on the frequency of channel opening and where they physically bind on the channel.

L-type Ca\(^{2+}\) channel antagonists have been studied for many years in other fields of application other than blockade of calcium entry through the L-type voltage-dependent Ca\(^{2+}\) channel. Historically, the literature in the field of L-type Ca\(^{2+}\) channel blockers is full of information concerning their effects on other sites that regulate Ca\(^{2+}\) movements into and within cells. Among these effects are blockade of Ca\(^{2+}\) pumps, Na\(^+\)/Ca\(^{2+}\) exchange, Na\(^+\)/K\(^+\) pump, protein kinase C, and mitochondrial respiration. These L-type Ca\(^{2+}\) channel blockers were reported to act as antihypertensive, antiangiogenic, antiarrhythmic, and antiplatelet agents. In addition, they were also reported to possess both immunosuppressive and antiinflammatory activity. The mechanism by which the L-type Ca\(^{2+}\) channels affect inflammation was difficult to be attributed to a specific target that modulates macrophage activation. An original explanation is now suggested in this issue of Circulation Research by Das et al., who elegantly demonstrated that both classes of L-type Ca\(^{2+}\) channel blockers, verapamil and amlodipine, suppressed macrophage activation-induced upregulation of plasminogen (Plg) binding and Plg receptor (Plg-Rs) expression. Furthermore, these authors clearly show that the Cav1.2 voltage-dependent L-type Ca\(^{2+}\) channel increased in differentiated macrophage, and deletion of this channel prevented the increase in Plg binding and Plg-Rs overexpression. These effects were shown to be associated with increase of intracellular Ca\(^{2+}\), stimulation of Ca\(^{2+}\) influx and probably intracellular Ca\(^{2+}\) release. In addition, Das et al also showed very convincing in vivo results that support their claims that the expression of Plg-Rs in macrophages is dependent on Cav1.2 voltage-dependent L-type Ca\(^{2+}\) channels. However, the most intriguing feature of the work of Das et al is that depolarization of the macrophage cell membrane with high extracellular K\(^+\) had no effect on the intracellular Ca\(^{2+}\) level of THP-1 cells. Because L-type Ca\(^{2+}\) channel blockers as well as knockout of Cav1.2, but not depolarization of the cell membrane, affect macrophage Ca\(^{2+}\) mobilization, thus the authors concluded that the increase of intracellular Ca\(^{2+}\) in activated macrophage is attributable to Ca\(^{2+}\) entry through Cav1.2 L-type Ca\(^{2+}\) channels that lack voltage dependency.

Considering the results of Das et al., their conclusion is without, any doubt, well justified and logical. However, most investigators believe that Cav1.2 represents the L-type Ca\(^{2+}\) channel, which is supposed to be voltage-dependent. Thus, the conclusion that Cav1.2 in macrophage is not voltage-dependent does not fit the conventional paradigm. Some biophysicists may not agree or understand how a voltage-dependent Ca\(^{2+}\) channel can lose its voltage dependency and still remain a Cav1.2 channel. One possibility is that macrophage L-type Ca\(^{2+}\) channel represents a different type of Cav1.2 that may lose its voltage dependency because of intracellular factor(s) that are present in macrophage or macrophage-like cells. Such a dependency of the biophysical characteristics of a voltage-dependent ionic channel on the intracellular milieu was reported for the voltage-dependent Na\(^+\) channel. However, another problem may allow some biophysicists to harden their opinions, because even if Cav1.2 expression increased, Das et al were not able to detect any inward Ca\(^{2+}\) current in macrophage. These biophysicists will have difficulty to correlate the convincing pharmacological and molecular results with those concerning the absence of the finger print of the L-type Ca\(^{2+}\) channel in macrophage. Some biophysicists would also argue by saying that the macrophage potential of macrophage is near −15 mV and even if the L-type is present, it will not be fully activated by voltage. Furthermore, they would say that membrane potential hyperpolarizes to near −90 mV after a few days of macrophage culturing and phagocytosis. These latter processes would induce changes in ionic channel currents and...
background currents such as activation of high conductance outward K\(^+\) current and Ca\(^{2+}\)-activated K\(^+\) channels (240 pS in symmetrical K\(^+\)).\(^{13,14}\) These types of ionic channels have also been reported to be blocked in macrophage by verapamil and the inorganic Ca\(^{2+}\) blocker, cobalt.\(^{13,14}\)

Furthermore, some scientists would argue that, as reported largely in the literature, increased intracellular Ca\(^{2+}\) is among the most important drivers of macrophage activation, and this increase can be attributable to one or several mechanisms regulating intracellular Ca\(^{2+}\) homeostasis such as blockade of Ca\(^{2+}\) pump, overload with intracellular Na\(^+\) attributable to blockade of the Na\(^+\)/K\(^+\) pump, and/or acidosis, which drives a Ca\(^{2+}\) influx through the Na\(^+\)/Ca\(^{2+}\) exchanger.\(^{4–6}\) As in macrophage,\(^{11}\) the L-type Ca\(^{2+}\) antagonists also block the Na\(^+\)/Ca\(^{2+}\) exchanger.\(^{4,6,8}\) This exchanger is also present at the nuclear membranes\(^1\) and could be also a target of some Ca\(^{2+}\) blockers. Thus, in a cell type where a biophysical study of the L-type Ca\(^{2+}\) channel was never demonstrated, the use of molecular biology techniques and/or L-type Ca\(^{2+}\) channel blockers, as pharmacological specific tools for studying such a channel, should be carefully interpreted.

Future research is likely to be fruitful in confirming the role of the L-type Ca\(^{2+}\) channel or L-type-like Ca\(^{2+}\) channel in macrophage and their role in inflammation.

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None.

**References**


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