CALCIUM CHANNEL INHIBITORS : ACTIONS ON SUBTYPES OF THE CA ION CHANNEL IN SMOOTH MUSCLE

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Calcium channel inhibitors act by occluding membrane ion channels that control entry of calcium ions into the cells of smooth muscle and the heart. They have found clinical use in the treatment of angina and cardiac dysrhythmias. Voltage dependent Ca channels are more susceptible to the Ca channel inhibitors than are receptor-operated channels (Bolton 1979). It is possible that these channels may exist in various subtypes, and we have investigated this using the rat vas deferens because this can be activated by a wide variety of different procedures.

Rat isolated vasa deferentia were suspended in Krebs-Henseleit solution at 37° and contractions obtained with KCl 160mM (producing phasic and tonic components), noradrenaline 30μM (producing fast and slow responses), single pulse nerve stimulation (producing a twitch having 2 phases) and prolonged contact with methoxamine 8.1μM or $BaCl_2$ 1mM (producing rhythmic contractions). All of these responses were abolished in Ca-free solution and blocked by $LaCl_3$, showing that they are dependent on Ca entering from the extracellular compartment, not on Ca release from intracellular stores. Voltage-dependent (type I) responses were susceptible to Ca channel inhibitors, the KCl tonic response being more sensitive than the KCl phasic response. This suggests that Ca channels are more readily occluded during sustained depolarisation. The remaining responses were less sensitive to the Ca channel inhibitors, type II (rhythmic contractions and phase 1 of the twitch) requiring 10-100 times higher concentrations than type I. A third type of response (noradrenaline fast component and phase 2 of the twitch) could be blocked by verapamil or methoxyverapamil but was totally resistant to nifedipine.

Table 1 IC_{50} values (μM)

Channel type	Nifedipine	Verapamil	Methoxyverapamil
I	0.03 - 0.3	0.7 - 1.6	0.8 - 1.6
II	1.6 - 3	30 - 152	14 - 75
III	no effect (14μM)	31 - 74	17 - 100

The results suggest that there are subtypes of the Ca ion channel. It is possible that future drugs will be able to distinguish between them more completely, resulting in greater specificity of action.

Bolton, T.B. (1979) Physiol. Revs. 59: 606-718

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