Molecular actions of fendiline, a unique Ca^{2+} channel blocker

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Fendiline, a diphenylalkylamine (DPA) type of antianginal drug, is reputed to have L-type Ca^{2+} channel (LTCC) blocking (CCB) as well as calmodulin inhibitory properties. Our whole-cell patch-clamp studies have shown that fendiline inhibits LTCC current (I_{CaL}) in isolated guinea pig ventricular myocytes and this inhibitory effect is overcome by isoproterenol (ISO), which increases the channel activity by cAMP dependent phosphorylation of the channel protein. ISO also antagonized the inhibition of I_{Cal} by other types of CCBs, viz. dihydropyridines (DHP, nifedipine), phenylalkylamines (PA, verapamil), and benzothiazepines (BTZ, diltiazem). Bay K 8644, a DHP type LTCC agonist (CCA), which directly activates the Ca^{2+} channels, also overcomes the inhibitory effect of these CCBs. However, Bay K 8644, failed to antagonize the inhibition of I_{CaL} by fendiline and instead caused an additional inhibition of LTCCs in its presence[1, 2]. It was further observed that isomer specific interactions (a well known feature of CCBs and CCAs) between fendiline and Bay K 8644 were not involved in this paradoxical conversion of the Ca^{2+} channel agonist activity of the latter into an antagonistic one by fendiline[3]. In the cell-attached patch-clamp studies on g. pig ventricular myocytes we observed that open probability of single channel LTCC activity (I_{Ba}) was strongly inhibited by fendiline isomers and the channel showed flickering activity in their presence. It is proposed that fendiline behaves as a unique type of CCB and acts on a site(s) different from the other types of CCBs. Moreover, fendiline has also been found to inhibit Na^+ channels[4] and $K_V4.x$ (transient outward) K^+ channels indicating its novel effects on the voltage gated cation channels. It is reported that fendiline, besides these ion channel modulating effects, also inhibits calmodulin activity and id1 promoter, modulates GABAB receptors and Ca^{2+} sensing receptors and increases intracellular Ca^{2+} in several cell types endowing it with unique pharmacological profile.

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