**Abstract**

Voltage-gated calcium channel blockers are widely used for the management of cardiovascular diseases, however little is known about their effects on cardiac cells in vitro.

We challenged neonatal ventricular cardiomyocytes (CMs) with therapeutic L-type and T-type Ca2+ channel blockers (nifedipine and mibefradil, respectively), and measured their effects on cell stress and survival, using fluorescent microscopy, Q-PCR and Western blot. Both nifedipine and mibefradil induced a low-level and partially transient up-regulation of three key mediators of the Unfolded Protein Response (UPR), indicative of endoplasmic (ER) reticulum stress. Furthermore, nifedipine triggered the activation of macroautophagy, as evidenced by increased lipidation of microtubule-associated protein 1 light chain 3 (LC3), decreased levels of polyubiquitin-binding protein p62/SQSTM1 and ubiquitinated protein aggregates, that was followed by cell death. In contrast, mibefradil inhibited CMs constitutive macroautophagy and did not promote cell death. The siRNA-mediated gene silencing approach confirmed the pharmacological findings for T-type channels.

We conclude that L-type and T-type Ca2+ channel blockers induce ER stress, which is divergently transduced into macroautophagy induction and inhibition, respectively, with relevance for cell viability. Our work identifies VGCCs as novel regulators of autophagy in the heart muscle and provides new insights into the effects of VGCC blockers on CMs homeostasis, that may underlie both noxious and cardioprotective effects.