**Abstract**

We have recently reported that human melanoma cells express a variety of voltage-gated calcium (Ca(2+) ) channel types, including low-voltage-activated T-type channels that play a significant role in melanoma cell cycle progression. Here, we challenged melanoma metastatic cells with T-type channel blockers of clinical use and found a dual effect on cell viability: (i) a reduction in the proliferation rate, through a halt in the progression to the G1 -S phase; and (ii) a promotion of cell death that was partially dependent on the activation of caspases. An in-depth analysis of the death process showed that the apoptotic pathway is preceded by endoplasmic reticulum stress and the subsequent inhibition of the basal macroautophagy which is active in these cells. The effects of pharmacological blockers on Ca(2+) homeostasis, autophagy, and cell death were mimicked by T-type channel gene silencing. These results provide the basis for a new pharmacological and/or gene silencing approach toward tackling melanoma metastasis.