Pharmacological modulation of BK channel improves cell viability under hyperkalemia condition

D. Tricarico[1], A. Mele[1], S. Calzolaro[1], G. Cannone[1], G.M. Camerino[1], M.M. Dinardo[1], R. Latorre[2], D. Conte Camerino[1]

[1]Dept. of Pharmacy-Drug-Science, University of Bari, Bari, Italy
[2]Centro de Neurociencias de Valparaíso, Facultad de Ciencias, Universidad de Valparaiso, Valparaiso, Chile

Emerging evidences suggest that Ca^{2+}activated-K^+-(BK) channel is involved in the regulation of cell viability. The changes of the cell viability observed under hyperkalemia (15 mEq/L) or hypokalemia (0.55 mEq/L) conditions were investigated in HEK293 cells expressing the hslo subunit (hslo-HEK293) in the presence or absence of BK channel modulators. The BK channel openers(10^{-11}-10^{-3}M) were: acetazolamide(ACTZ), dichlorphenamide(DCP), methazolamide(MTZ), bendroflumethiazide(BFT), ethoxzolamide(ETX), hydrochlorthiazide(HCT), quercetin(QUERC), resveratrol(RESV) and NS1619; and the BK channel blockers($2x10^{-7}$M-$5x10^{-3}$M) were: tetraethylammonium(TEA), iberiotoxin(IbTX) and charybdotoxin(ChTX). Experiments on cell viability and channel currents were performed using cell counting Kit-8 and patch-clamp techniques, respectively. Hslo whole-cell current was potentiated by BK channel openers with different potency and efficacy in hslo-HEK293. The efficacy ranking of the openers at -60 mV(Vm) was BFT> ACTZ >DCP ≥RESV≥ ETX> NS1619> MTZ≥ QUERC; HCT was not effective. Cell viability after 24 h of incubation under hyperkalemia was enhanced by 82±6 % and 33±7 % in hslo-HEK293 cells and HEK293 cells, respectively. IbTX, ChTX and TEA enhanced cell viability in hslo-HEK293. BK openers prevented the enhancement of the cell viability induced by hyperkalemia or IbTX in hslo-HEK293 showing an efficacy which was comparable with that observed as BK openers. BK channel modulators failed to affect cell currents and viability under hyperkalemia conditions in the absence of hslo subunit. In contrast, under hypokalemia cell viability was reduced by -22±4 % and -23±6 % in hslo-HEK293 and HEK293 cells, respectively; the BK channel modulators failed to affect this parameter in these cells. In conclusion, BK channel regulates cell viability under hyperkalemia but not hypokalemia conditions. BFT and ACTZ were the most potent drugs either in activating the BK current and in preventing the cell proliferation induced by hyperkalemia. These findings may have relevance in disorders associated with abnormal K^+ ion homeostasis including periodic paralysis and myotonia. Supported by Telethon GGP10101.