

Shi-Bing Yang

Block of potassium channels by haloperidol and its related compounds

Haloperidol is known as an antagonist of dopamine D2 receptors. Chronic haloperidol treatment produces many side effects including diabetes mellitus, torsade de pointes and rare but lethal malignant neuroleptic syndrome. Besides its D2 antagonism effect, it also blocks a variety of ion channels, however, at concentrations above therapeutical range. In this study, we assessed the pharmacological effect of haloperidol and one of the major metabolite, reduced-haloperidol on pancreatic ATP-sensitive potassium channel (KATP) and neuronal delayed-rectifier potassium channels (KDR) by using the whole-cell patchclamp technique. Significant portion of KATP and KDR currents were blocked by haloperidol and other related compounds, however, D2 receptor signaling pathway was not involved, since both D2 agonists and antagonists blocked these channels. The binding site of haloperidol and reduced-haloperidol was on the external surface of the channel pore as can be deduced from its blocking kinetics and sensitivity to $[K^+]_o$. 4-chlorophenyl-4-hydroxypiperidine (4C4HP) is the active fragment of haloperidol, as other compounds containing this moiety also blocked potassium channels. The potency of 4C4HP fragment positively correlated with the hydrophobicity index of the compound tested. We conclude that haloperidol block of potassium channels might be clinical relevant under certain condition. The ATP sensitivity of pancreatic KATP channel was also addressed in this study. We found that the KATP channel in β -cell in tissue slices had lower sensitivity to intracellular ATP than in conventional cultured cell. The IC_{50} of ATP to block KATP channel in tissue slices was estimated up to 1.4 mM, close to physiological $[ATP]_i$. The modulation on the SUR1 receptor, a compulsory KATP channel accessory subunit, might explain the reduction in sensitivity.