Investigation of The Effects of Blocking of Potassium Channels with 4- Aminopyridine on Paclitaxel Activity in Breast Cancer Cell Lines

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Abstract

Paclitaxel (PTX) has been used as a chemotherapeutic agent for several malignancies including breast cancer and efforts to increase the efficiency of PTX are continuing. In this study, FDA-approved 4-aminopyridine (4-AP), a voltage-gated potassium channel blocker, was used in combination with PTX in MCF-7 and MDA MB 231 cell lines it has been confirmed that K⁺ (potassium) channels are involved in the cell cycle. Viability was determined with trypan blue, a clonogenic assay was performed, and the cell cycle was determined with a flow cytometer and immunochemistry. To gain an insight into the mechanism, intracellular K⁺ concentration, intracellular Ca²⁺ (calcium) concentration, and transmembrane potential measurements were made with corresponding fluorescent dyes. Apoptotic cell number was determined using Annexin /PI method by flow cytometer. Viability decreased with combination therapy and the clonogenic assay proved decreased colony formation. Apoptotic cell number was increased after treatment with the combination in both cell lines. Cell cycle measurements showed G1 arrest for both MCF-7 and MDA MB 231 cell lines upon 4-AP treatment. PTX caused G1 arrest in MCF-7 cells and S phase arrest in MDA MB 231 cells. Combination treatment caused S phase arrest in MCF-7 cells and S phase and G2/M phase arrest in MDA MB 231 cells. Intracellular K⁺ concentration was increased after all treatments in both cell lines. Ca²⁺ concentration was increased significantly after combination treatment. Depolarization in the transmembrane potential was observed after all treatments in both cell lines. Biophysical parameters like the transmembrane potential and ion fluxes have been defined in cancer progression which can provide new aspects for cancer treatments. This study shows that the combination of 4-AP with PTX is a promising alternative the mechanism of which needs further investigation considering the results obtained for Ca²⁺, K⁺, and membrane potential.

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