MELATONIN SYNERGISTICALLY ENHANCES CISPLATIN-INDUCED APOPTOSIS VIA THE DEPHOSPHORYLATION OF ERK/P90 RIBOSOMAL S6 KINASE/HEAT SHOCK PROTEIN 27 IN SK-OV-3 CELLS

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To evaluate melatonin's ability to enhance ovarian cancer cells to cisplatin treatment for ovarian cancer, this study was performed. Melatonin by itself had no significant cytotoxicity against SK-OV-3 cells, while cisplatin suppressed the cell viability in a dose-dependent manner. Combined treatment with cisplatin and melatonin synergistically inhibited the viability of SK-OV-3 cells with the synergism between two drugs (CI > combination index). In contrast, melatonin revealed the protective effect against cisplatin-induced cytotoxicity in OSEN normal ovarian epithelial cells. Cotreatment with cisplatin and melatonin increased the sub-G1 DNA contents and TdT-mediated dUTP nick end-labeling (TUNEL)-positive cells compared with cisplatin control in SK-OV-3 cells, suggesting that melatonin augments cisplatin-induced apoptosis. Consistently, combined treatment of cisplatin and melatonin increased the cleavage of caspase-3 and poly-(ADP-ribose) polymerase (PARP). Importantly, melatonin synergistically inhibited the phosphorylation of extracellular signal-regulated kinase (ERK) along with dephosphorylation of 90-kDa ribosomal S6 kinase (p90RSK) and heat shock protein 27 (HSP27) induced by cisplatin. Furthermore, melatonin remarkably blocked the expression and colocalization of p90RSK and HSP27 by combination treatment with cisplatin. Taken together, our findings demonstrate that melatonin enhances cisplatin-induced apoptosis via the inactivation of ERK/p90RSK/HSP27 cascade in SK-OV-3 cells as a potent synergist to cisplatin treatment.