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Synergistic effects of melatonin and other biological molecules on breast cancer MCF-7 cell functions: possible implications in anticancer therapy

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In the recent years, the antineoplastic action of melatonin has been extensively described, including oncostatic effects on different tumors and improvement of chemotherapeutic regimens. However, the mechanisms underlying these phenomena remain unclear and a matter of debate.

The aim of the present study was to further investigate the effects of melatonin, administered alone or in combination with other molecules, such as somatostatin and retinoic acid, on MCF-7 human breast cancer cells, in terms of cell viability, proliferation and death.

Melatonin 1 μM, 10 μM, 100 μM was administered for 24, 48, 72 hours. It was found that melatonin induced a dose and time-dependent inhibition of cell viability, as judged by MTS assay. This effect was particularly evident at pharmacologic concentration and was greatly potentiated when melatonin was given in association with somatostatin and retinoic acid, suggesting a synergistic effect of these molecules. We also showed that the reduced cell viability in the cells treated with the highest concentration of melatonin, either alone or in combination with somatostatin and retinoic acid, was associated with alteration in the cell cycle, with a reduced number of cells expressing cyclin A. Consistent with these latter data, the treated cells showed alteration in Notch/ Jagged signalling and a significant induction of necrotic cell death.

The electrical properties of the treated cells were also analyzed by whole patch clamp in voltage- clamp condition. Melatonin induced a decrease of the fast delayed rectifier K+ current and an increase of the slower activating Ca2+-dependent K+ current. Such effects were potentiated when melatonin was given in association with somatostatin and retinoic acid.

Taken together, these findings demonstrate, for the first time, that the oncostatic effect of melatonin on MCF-7 cells may be greatly increased by its association with somatostatin and retinoic acid and suggest that these effects are related, at least in part, to changes in the K+ channels type expression and functionality, in cyclin A expression and Notch pathway. These novel findings rise the intriguing hypothesis that melatonin in association with somatostatin and retinoic acid might prove helpful as adjuvant in breast cancer therapy.

Key words
MCF-7 cells, melatonin, retinoic acid, somatostatin, cell proliferation, cell death