MELATONIN MODULATION OF RADIATION AND CHEMOTHERAPEUTICS-INDUCED CHANGES ON DIFFERENTIATION OF BREAST FIBROBLAST

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INTRODUCTION

Melatonin is the main hormone secreted by the pineal gland. Melatonin production is regulated by photoperiod insofar as its synthesis and secretion are regulated by light but reduced at night in response to darkness. Estradiol, the main biologically active sex hormone present in breast tissue, plays a very important role in the genesis and progression of the tumor in women. For this reason, it is also possible to consider estradiol as a "breast carcinogen". Modulation by melatonin of the desmoplastic reaction stimulates the differentiation of fibroblasts to adipocytes, decreases the aromatase activity of adipocytes, inhibiting the expression of antiadipogenic cytokines.

OBJECTIVE

The main objective of this work is to study the effects exerted by chemotherapeutics, docetaxel and vinorelbine, and radiation on the differentiation of human mammary preadipocytes and the modulation of these effects by melatonin.

MATERIALS & METHODS

CULTURE CONDITIONS

Human breast preadipocytes (BBF) were cultured until reaching confluence in preadipocyte Medium (PM-1) supplemented with penicillin and streptomycin in a humid atmosphere and they were differentiated into adipocytes with Adipocyte Differentiation Medium (ADM-2).

IONIZING RADIATION TREATMENT

Both cell lines were exposed to X-irradiation using a model YXON SMART 200 tube at room temperature. We used 8 Gy radiation as the optimal radiation dose.

MEASUREMENT OF CELLULAR PROLIFERATION

Cell proliferation was measured by the MTT Method. We used the reduction of tetrazolium salts and, at the end, we read absorbance at 570 nm.

RESULTS & DISCUSSION

Docetaxel and vinorelbine reduced cell proliferation and increased the triglyceride content of adipocytes (treated or not during its differentiation), an indicator of adipogenic differentiation. In both cases, melatonin potentiated the effects of docetaxel and vinorelbine. The presence of malignant epithelial cells decreased triglyceride content. Docetaxel and vinorelbine increased adipogenic differentiation. Melatonin 1 mM stimulated adipogenesis differentiation and potentiated the stimulatory effect induced by docetaxel and vinorelbine.

IONIZING RADIATION (in adipocytes and in co-cultures) reduced cell proliferation and intracellular triglyceride content. Melatonin decreased cell proliferation and counteracted the effect of radiation and increased adipogenesis differentiation.

Docetaxel and ionizing radiation decreased aromatase activity and the expression of aromatase and aromatase promoter II. Melatonin inhibited aromatase activity and the expression of aromatase, aromatase promoter I and II and even more in the presence of docetaxel and radiation.

Docetaxel inhibited the mRNA expression of all three antiadipogenic cytokines, in combination with melatonin increased the inhibition. Vinorelbine only reduced TNFα and IL-1β expression, and in the presence of the melatonin the reduction was even more. Radiation increased TNFα mRNA expression and the melatonin counteracted the stimulatory effect. Melatonin alone induced a reduction of the three cytokines.

CONCLUSIONS

- Melatonin potentiates the stimulatory effect of chemotherapeutics on the differentiation of preadipocytes in mature adipocytes by increasing their stimulatory effect on C/EBPα and PPARγ and by increasing the downregulation of antiadipogenic cytokines, TNF-α, IL-6 and IL-1β.
- In combination with radiation, melatonin counteracts the inhibitory effect of radiation on differentiation of preadipocytes, by increasing C/EBPα and PPARγ expression and by decreasing the TNFα expression induced by radiation.
- Docetaxel and ionizing radiation reduce the activity and expression of aromatase in breast fibroblasts. Melatonin potentiates that inhibitory effect by increasing the downregulation of aromatase promoter II and cyclooxygenases expression.