

ANTITUMORAL ACTION OF ROSIGLITAZONA. *IN VIVO* AND *IN VITRO* STUDIES.

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Thiazolidinediones are widely used for treatment of type 2 diabetes mellitus. Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor superfamily. PPAR γ is of particular interest because it is (has been) implicated in several human pathological situations, including diabetes and cancer. Current studies looking for more effective treatments, point out thiazolidinediones (e.g. rosiglitazone (Rosi)) as possible antitumoral agents.

Current studies propose*/indicate a possible role of thiazolidinediones (e.g. rosiglitazone (Rosi)) as antitumoral agents.

The aim of our investigation was to study the action of Rosi in comparison with the antiestrogen tamoxifen (Tam). *In vivo* and *in vitro* studies were performed. We evaluated the effect of Rosi (0,06 mg/kg/day) and Tam (1mg/kg/day) on rats bearing mammary tumors induced by three ip doses of the carcinogen N-Nitroso-N-Metilurea. Rats basal glicemia, insulin levels and glucose tolerance test were not modified by Rosi treatment.

The results obtained showed that Rosi treatment produces the growth inhibition of 45% of the tumors vs 55% of regression produced by Tam ($P < 0,0001$ vs controls without any treatment). Combined treatment (Rosi+Tam) produced the regression of 75% of tumors.

The effect of Rosi was assayed on mammary carcinoma cell lines: MCF-7 (ER+) and MDA-MB-231 (ER-) employing the clonogenic assay. Results showed a significant dose-dependent inhibition of cell proliferation induced by Rosi. On MCF-7 cells, results indicated a EC50 value of 20 μ M and 0.4 μ M for Rosi and Tam, respectively. On MDA-MB-231 cells, the EC50 were 30 μ M and 5 μ M for Rosi and Tam, respectively. The *in vitro* combined treatment indicated that the inhibition of cell growth was significantly more important in MFC-7 cells (Rosi 20 μ M+Tam 1 μ M) than in MDA-MB-231 cells (Rosi 30 μ M+Tam 5 μ M). The analysis of cell cycle by flow cytometry, clearly demonstrated that Rosi produced a cell arrest in G0/G1 phase for both MCF-7 cells (at 48 hs) and MDA-MB-231 (at 24 hs).

Our findings suggest that Rosi would act through both ER and PPAR γ receptors. This findings have significant implications because can open new strategies on the treatment of breast cancer.