No effect of the PPAR-gamma agonist rosiglitazone on ACTH or cortisol secretion in Nelson's syndrome and Cushing's disease in vitro and in vivo.

Abstract:

OBJECTIVE: Surgical tumor resection remains the primary treatment strategy in ACTH-secreting pituitary adenomas, i.e. Cushing's disease (CD) and Nelson's syndrome (NS). However, an effective long-term pharmacological regime is not available in patients with persistent ACTH-hypersecretion. The nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-gamma) is abundantly expressed in most pituitary adenomas. First encouraging data reported that the PPAR-gamma ligand rosiglitazone antagonizes ACTH hypersecretion and exerts also antiproliferative effects in pituitary cell lines. Herein, we studied the potential therapeutical effects of rosiglitazone in patients with ACTH-secreting pituitary adenomas in vitro and in vivo. MATERIALS AND METHODS: Seven patients with persistent ACTH-hypersecretion (3 with NS, 4 with persistent CD) were treated 5 months with rosiglitazone (4 - 16 mg/day). In vitro assays were performed in primary cell cultures obtained from eight additional patients with ACTH-secreting pituitary adenomas applying 80 microM rosiglitazone repeatedly over a time period of 14 days. RESULTS: Our long-term clinical trial with the PPAR-gamma-activator rosiglitazone showed no amelioration of clinical symptoms nor an inhibiting effect on ACTH-secretion in vivo. In vitro, rosiglitazone treatment led to a
statistically significant decrease of ACTH levels in 2 out of 8 primary cell cultures after 14 days compared to untreated controls. CONCLUSION: In contrast to the initially promising laboratory data gathered in pituitary cell line experiments and nude mice models, our experimental data obtained in primary human ACTH-expressing pituitary adenoma cell cultures as well as our clinical experience with a long-term rosiglitazone trial in approved antidiabetic doses support the recently reported disappointing reports on acute or short-term medical treatment of ACTH-hypersecretion with PPAR-gamma activators.