Steroid synthesis inhibition with ketoconazole and its effect upon the regulation of the hypothalamus-pituitary-adrenal system in healthy humans.

Abstract:
Steroid synthesis inhibitors are commonly used in the treatment of patients with Cushing's disease, but may also improve psychopathology in hypercortisolemic depressed patients. Since glucocorticoids exert a negative feedback at pituitary and supra-pituitary levels, the inhibition of steroid synthesis may lead to increased expression of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). We studied the effect of treatment with 800 mg ketoconazole (3 weeks) upon the concentrations of basal plasma cortisol in the evening, corticosteroid-binding globulin (CBG), dehydroepiandrosterone-sulfate (DHEA-S), and ACTH as well as the concentrations of cortisol, CRH, and AVP in cerebrospinal fluid (CSF) at 8.30 h in 10 healthy, male volunteers. While we found cortisol plasma concentrations to be unchanged, we noted a significant increase in ACTH (post: 45.1 +/- 43.5; pre: 14.2 +/- 5.2 pmol/l; F(1,8)=9.78, p<0.02) and CBG concentrations (post: 38.8 +/- 4.3; pre: 31.9 +/- 4.2 microg/l), but DHEA-S plasma concentrations declined (post: 1.75 +/- 1.83; pre: 2.75 +/- 2.80 mg/l; F(1,8)=7.9, p<0.03). CRH concentrations in CSF were unchanged after treatment (post: 62.5 +/- 15.9; pre: 63.7 +/- 13.9 pg/ml), while there was a trend for AVP concentrations to rise during treatment...
(post: 2.52 +/- 1.18; pre: 1.92 +/- 0.96 pg/ml; paired t=-1.9, p<0.1). Cortisol CSF concentrations declined in the elderly (pre: 52.5 +/- 23.2; post: 26.7 +/- 4.6 nmol/l), but not in the young subgroup (pre: 15.6 +/- 11.3; post: 27.7 +/- 9.4 nmol/l). We thus conclude that the treatment of healthy controls with steroid-synthesis inhibitors does not lead to a major increase in CRH secretion.