The influence of hormone replacement therapy on the serotonin-1A receptor binding in postmenopausal women
A longitudinal study using Positron Emission Tomography (PET) and the radioligand [carbonyl-11C]WAY-100635

Georg S. Kranz¹, Andreas Hahn¹, Johanna Ungersböck², Ulrike Kaufmann³, Patrycja Stein¹, Pia Baldinger¹, Anna Höflich¹, Sylwia Zgud¹, Markus Mitterhauser², Wolfgang Wadsak², Siegfried Kasper¹, Rupert Lanzenberger¹

¹ Department of Psychiatry and Psychotherapy, ² Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology, Medical University of Vienna, Austria.

Background:
The serotonin-1A receptor (5-HT₁A) is involved in the etiology and therapy of major depressive and anxiety disorders. Animal studies have shown a strong effect of steroid hormones on the 5-HT₁A receptor expression [1], the main inhibitory serotonergic receptor subtype modulating serotonergic neurotransmission.

Objectives:
To investigate the influence of changes in steroid hormone plasma levels induced by hormone replacement therapy (HRT) on presynaptic 5-HT₁A receptor binding in the midbrain region including the raphe nuclei. To investigate the relationship of cortisol and the postsynaptic 5-HT₁A BPND in postmenopausal women.

Methods:
Randomized, double-blind, cross-sectional, longitudinal study. 19 postmenopausal subjects, aged 55.26 ± 4.98 (mean±SD) underwent PET twice using [carbonyl-11C]WAY-100635. Medication: (1) oral estrogen (17β-estradiol valerate) and micronized progesterone; (2) oral estrogen (17β-estradiol valerate) and two placebos (matched).

Results:
Subjects showing a distinct suprathreshold increase in E plasma level (PET₁=10.1±3.3pg/ml, PET₂=108.1±83.1pg/ml) but not P (group 1, n=8) showed an elevation (+31.8%) in 5-HT₁A BPND within the midbrain raphe region after 8 weeks of treatment (PET₁=0.85±0.33, PET₂=1.12±0.31, t=−2.63, p=0.034; paired samples t-test).

Conclusions:
Our results indicate that E replacement therapy elevates 5-HT₁A receptor BPND, whereas P seems to counter this effect, since E+P combination therapy showed no change in 5-HT₁A BPND. The up-regulation of 5-HT₁A autoreceptors in the midbrain by E reflects a compensatory mechanism in view of the fact that E has been observed to increase the level of serotonin in the dorsal raphe nuclei [2]. A down-regulation in autoreceptor BP by P, as indicated by our results, concurs with preclinical research, showing that P influences serotonergic neurotransmission by transrepressing the 5-HT₁A receptor promoter, and thereby reducing the 5-HT₁A receptor expression [1, 3]. The increase of 5-HT₁A autoreceptors demonstrates the therapeutic potential of E treatment, given the frequently found decrease in 5-HT₁A binding in major depressive disorders.

We previously showed a strong negative correlation between cortisol plasma levels and postsynaptic 5-HT₁A BPND in patients with social anxiety disorder but not in healthy control subjects [4]. Our results therefore reflect an increased vulnerability for mood disorders in untreated postmenopausal women.

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References: