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*-^{11}C]WAY-100635

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Background:

The serotonin-1A receptor (5-HT$_{1A}$) 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-HT$_{1A}$ 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-HT$_{1A}$ receptor binding in the midbrain region including the raphe nuclei. To investigate the relationship of cortisol and the postsynaptic 5-HT$_{1A}$ BP$_{ND}$ 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-^{11}C]WAY-100635. Medication: (**1**) oral estrogen (17β-estradiol valerate) and placebo; (**2**) oral estrogen (17β-estradiol valerate) and micronized progesterone; (**3**) two placebos (matched).

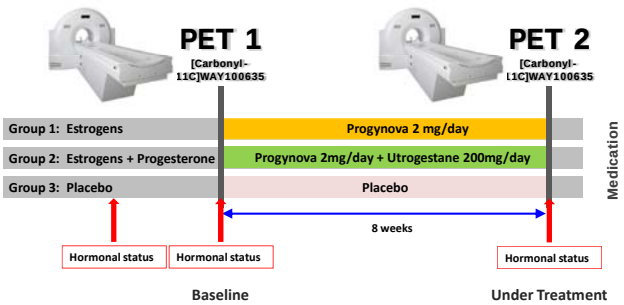

Figure 1: Study design

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-HT$_{1A}$ BP 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).

No significant change in 5-HT$_{1A}$ BP$_{ND}$ (*p*>0.1) was observed for the group showing a plasma level increase in both E and P (group **2**, n=5) and in BP$_{ND}$ for the placebo group (group **3**, n=6).

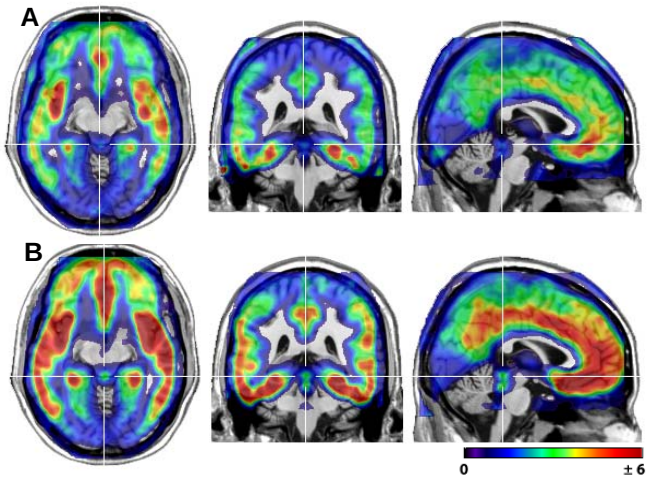

Figure 2: Estrogen (E) replacement therapy induced increase in 5-HT$_{1A}$ autoreceptor binding within the midbrain raphe nuclei (crosshair). Distribution maps of 5-HT$_{1A}$ receptor BP$_{ND}$ of a single subject, (**A**) before and (**B**) after eight weeks of hormone replacement therapy, superimposed on triplanar structural images.

Furthermore, correlation analysis including all subjects revealed that 5-HT$_{1A}$ receptor BP$_{ND}$ in the amygdala was negatively associated with cortisol plasma levels at baseline (r= - 0.65, p=0.003).

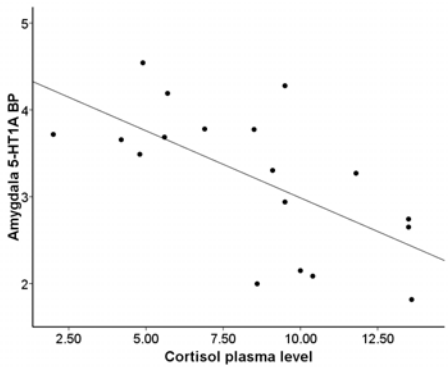

Figure 3: Negative (r=-0.67) association between amygdala BP$_{ND}$ and cortisol plasma levels at baseline

Conclusions:

Our results indicate that E replacement therapy elevates 5-HT$_{1A}$ receptor BP$_{ND}$, whereas P seems to counter this effect, since E+P combination therapy shows no change in 5-HT$_{1A}$ BP$_{ND}$. The up-regulation of 5-HT$_{1A}$ 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 nucleus [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-HT$_{1A}$ receptor promoter, and thereby reducing the 5-HT$_{1A}$ receptor expression [1, 3]. **The increase of 5-HT$_{1A}$ autoreceptors demonstrates the therapeutic potential of E treatment, given the frequently found decrease in 5-HT$_{1A}$ binding in major depressive disorders.**

We previously showed a strong negative correlation between cortisol plasma levels and postsynaptic 5-HT$_{1A}$ BP$_{ND}$ 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**.

Disclosure:

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References:

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