Anti-neuropeptide Y plasma immunoglobulins are distinctly associated with altered mood and appetite in depressive disorder

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### Introduction
Neuropeptide Y (NPY) has potent antidepressant and orexigenic properties suggesting that altered NPY signaling can be relevant to etiology of altered mood and appetite commonly co-occurring in depressive disorder. Levels of NPY are altered in patients with depression. Autoantibodies (autoAbs) directed against NPY are present in humans and rats and hence may interfere with the NPY signaling relevant to regulation of mood and feeding behavior. In this work, we studied if depressive patients display altered levels or affinities of NPY autoAbs. We also developed animal models to evaluate the effects of NPY autoAbs in depression-like and feeding behavior.

### Materials and methods

**Sera:** 14 men with mild depression (MID); 9 men with moderate depression (MOD); 20 healthy males (Control).

Study subjects were evaluated by the Montgomery and Åsberg Depression Rating Scale (MADRS)

**ELISA**

Assay of serum levels of total and free IgG, IgM and IgA autoAbs reactive with NPY

**BlAcore**

Affinity assay for NPY of purified total IgG and IgM autoAbs from patients and controls

#### Animal models

- Peripheral injection (iv): purified patient’s and control’s IgG
- Brain injection (icv): patients’ or Rb IgG

### Results

#### Anti-NPY IgG in Human subjects

**Figure 1. Plasma levels of anti-NPY IgG autoAbs**

MOD patients show reduced anti-NPY IgG levels when compared to MID and controls (Figure 1, ANOVA, p=0.02). Tukey's post test *p<0.05, Student's t-test p<0.05). Levels of anti-NPY IgG correlate to MADRS scores (Figure 2, Pearson’s r = -0.33, p<0.05). Affinity values of IgG and IgM autoAbs for NPY autoAbs showed 100 folds variability among patients and controls, but the group means were not significantly different (Figure 3). Affinity of IgG autoAbs for NPY correlated negatively to BMI (Figure 4, Pearson’s r = -0.31, p<0.05).

**Figure 2. Correlation of depression severity and Anti-NPY IgG levels**

**Figure 3. Affinity of IgG for NPY**

**Figure 4. Correlation of BMI and affinity of anti-NPY IgG autoAbs**

**Figure 5. FST after iv IgG injections and correlation between plasma levels of NPY IgG and MADRS**

**Figure 6. FST after icv injection of NPY and patient’s or Rb IgG**

**Figure 7. Food intake after icv injection of NPY and patient’s or Rb IgG**

Peripheral injection of purified IgG increased immobility time vs. saline (Figure 5A, ANOVA, p=0.04, Student's t-test *p<0.05, **p<0.01), but no differences were found between three subjects' groups. A negative correlation was found between anti-NPY IgG levels and immobility time (Figure 5B, Pearson’s r = -0.36, p<0.05). Mice receiving icv Rb anti-NPY antibody or purified patient’s IgG with high and low affinity for NPY had less reduction of immobility time when compared to the group receiving only NPY (Figure 6; ANOVA, p=0.004, Tukey's post-test * p<0.05, **p<0.01, Student's t-test #p<0.05). Food intake was lower in mice treated with patient’s IgG or Rb anti-NPY IgG when compared to NPY only group and a significant difference was found between high and low NPY affinity groups (Figure 7 A and B; ANOVA K.W., p<0.0001, Dunn's post-tests **p<0.01, Student’s t-tests #p<0.05.)

### Conclusions
This is the first study evaluating autoAbs against NPY in depressed patients. A decrease in plasma levels of NPY IgG autoAbs but not changes of their affinities is directly associated with severity of depression as shown in patients with moderate depression and in animal models of passive transfer of autoAbs. In contrast, lower affinity of IgG autoAbs for NPY is associated with higher appetite and BMI. These data suggest that changes of plasma levels of anti-NPY autoAbs are relevant to altered mood, while changes of their affinity may be involved in altered appetite in depressive disorder.