**ABSTRACT**

Despite the increasing variety of antidepressant (AD) drugs currently available, only a third of depressed patients respond adequately to the treatment, and up to half of them relapse within one year. Therefore, there is a pressing need to identify predictive biomarkers of treatment outcome. In the present study, we focused on the identification of 15 genes involved in HPA axis functionality, inflammation and neuroplasticity in blood monocytes of depressed patients (n = 76) and controls (n = 76). Prior to and after 8 weeks of AD treatment with escitalopram or nortriptyline (GENDEP study), 15 genes involved in HPA axis functionality, inflammation and neuroplasticity were assessed by using a Nanodrop spectrometer and Agilent Bioanalyzer. Two microarrays were performed for Real Time PCR analyses using HOT FIREPol® EvaGreen® qPCR Mix (Solis BioDyne, Tartu, Estonia). The study confirms previous evidence that increased levels of pro-inflammatory cytokines, IL-1β (+48%, F=117.9, p<0.0001), IL-6 (+24%, F=37.3, p<0.0001) and TNF-α (+77%, F=24.0, p<0.001) and decreased GR levels (F = 6.08, p = 0.049), were higher in non-responders (“predictors”) and lower in responders vs. non-responders, while changes over time were analyzed using the General Linear Model (GLM) according to a repeated-measure design, with time (T1, T2) and response (yes/no) as within-subject factors.

**METHODS**

- Change in biomarkers (“targets”) during antidepressant treatment and in relation with antidepressant response
- Biomarkers differences between patients at baseline, and controls
- Non-responders had higher mRNA levels of the three pro-inflammatory cytokines, IL-1β (+77%, F=24.0, p<0.001), IL-6 (+24%, F=37.3, p<0.0001) and TNF-α (+77%, F=24.0, p<0.001). Indeed, expression levels of pro-inflammatory molecules like KDNC have been found reduced in depressed patients (5).

**RESULTS**

- Baseline differences in biomarkers between responders and non-responders (“predictors”)

**CONCLUSIONS**

- Our main finding is that the expression levels of three pro-inflammatory cytokines, namely IL-1β, TNF-α and MIF predict the antidepressant treatment response. In particular we found that the best predictive model was when we included all the three cytokines in the linear regression, suggesting that they tip in both similar and different molecular mechanisms. Moreover, we found that these genes are both aberrant in depressed patients (vs. controls) and are normalized by antidepressant treatment, but not in connection with antidepressant response at least within the 8 weeks time-frame, suggesting that some biological abnormalities in depression are targeted by antidepressants pharmacological action but also in patients who are not improving.

- Finally, a normalization of FKBP-5 levels in depressed patients only suggest that depression is characterized by the coexistence of higher FKBP-5, and lower GR, leading to GR resistance, and that antidepressant treatment require normalization of GR function via normalization of both genes.

**BACKGROUND**

- Despite the increasing variety of antidepressant therapies currently available, only a third of depressed patients respond adequately to the treatment, and up to half of them relapse within one year. Unfortunately, we still cannot predict the likely of response of an individual patient to a specific drug. Therefore, there is a pressing need to identify predictive biomarkers of treatment outcome.

- Based on the current conceptualization of the disorder, we suggest that hypothalamus-driven blood-based biomarkers analyses should focus on the biological systems that have been more commonly described as abnormal in depression: the glucocorticosteroid receptor (GR) complex, inflammation and neuroplasticity (1).

- One of the most consistent biological findings in depression is an upregulation of the hypothalamic-pituitary-adrenal (HPA) axis, as a multitude of studies describing high levels of cortisol, the main HPA axis hormone, in the context of a reduced function of the GR, the cortisol receptor primarily involved in HPA axis regulation during stress. Moreover, this reduced GR function, or glucocorticosteroid resistance, is particularly evident in patients with treatment-resistant depression (2), and indeed persistent glucocorticosteroid resistance during antidepressant treatment is associated with early relapse (3).

- A second biological system involved in the antidepressant response is inflammation. Pro-inflammatory cytokines, and in particular interleukin IL-1β, IL-6 and TNF-α, are increased in depressed patients as compared to controls. In both antidepressants have been shown to have anti-inflammatory effects, and anti-inflammatory drugs, such as cicleson and TNF-α antagonists, have been shown to have antidepressant properties (4).

- Finally, one of the potential mechanisms by which successive HPA axis activity and inflammatory responses may contribute to the pathogenesis of depression is through inhibition of neurotrophic factors and hence disturbance of neuroplasticity. Indeed expression levels of neuroplastic molecules like BDNF have been found reduced in depressed patients (5).

- We found increased levels of MIF (F = 0.247, p < 0.0001), IL-1β (F = 1.58, p = 0.045), TNF-α (F = 0.778, p = 0.018), IL-6 (F = 2.44, p = 0.028) and FKBP-5 (F = 4.04, p = 0.014) in depressed patients as compared to controls. Furthermore, in the group of depressed patients we also observed reduced GR expression (F = 0.86, p = 0.001), and increased BDNF levels (F = 0.46, p = 0.032), but no differences in FKBP-5 (F = 0.166, p = 0.681).

**CONFLICT OF INTEREST**

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