Biomarkers of inflammation and neural plasticity in olfactory neuroepithelium-derived cells from patients with major depressive disorder

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Background

Growing evidence suggests a significant role of inflammation and neural plasticity processes in the pathogenesis of major depressive disorder (MDD) [1,2]. The olfactory mucosa, closely related to the central nervous system, allow the non-invasive, low-cost study of new biomarkers and therapeutic targets for neuropsychiatric diseases [3]. However, a revision of the literature has shown only a few studies about novel biomarkers of MDD using cell cultures from the olfactory neuroepithelium (ON). The aim of this work was to determine the diagnostic value of inflammatory and neural plasticity markers (MAPK14, IL6, TNF-a, Mecp2, BDNF, GSK3, GRIA2 and FosB) in MDD, and to study their relationship with demographical, course and clinical variables.

Methods

Subjects:

- N: 12 patients with MDD (DSM-IV criteria) and 7 healthy controls
- Exclusion criteria: other Axis I mental disorders (patients) or any mental disorder (controls) (assessed with the MINI), inflammatory diseases.

Clinical Assessment:

- Demographical, course and clinical variables.
- Clinical assessment: *Hamilton Depression Rating Scale* (HDRS), *State-Trait Anxiety Inventory* (STAI), *Holmes-Rahe Social Readjustment Rating Scale*, *Perceived Stress Scale* (PSS) and *World Health Organization Disability Assessment Schedule* (WHODAS 2.0).
- Treatment resistance assessment: Thase and Rush staging method

Olfactory neuroepithelium cells biomarkers:

mRNA was isolated from ON cells and MAPK14, IL6, TNF-a, Mecp2, BDNF, GSK3, GRIA2 and Fos-B gene expression levels were quantified using quantitative polymerase chain reaction (q-PCR).

Statistical analysis:

Shapiro-Wilk test was used to assess the normality of the data. Qualitative variables were analyzed with Fisher exact test and differences in quantitative variables with one-way ANOVA. The Pearson's correlation was performed for determining the relationship between the mRNA biomarkers levels and demographical, course and clinical variables.

Results

Demographic and clinical data: (Table 1)

	Controls Mean (SD)	MDD patients Mean (SD)	p
Age—years	43.29 (11.23)	49.42 (8.12)	NS
Sex—no. (%)			NS
Male	4 (57.1)	6 (50)	
Female	3 (42.9)	6 (50)	
Age at onset (years)		30.67 (13.10)	
Episode duration (months)		13.75 (16.82)	
Thase-Rush staging method		3.25 (1.65)	
HDRS	0.14 (0.37)	22.75 (4.18)	< 0.001
STAI			
State anxiety	7.71 (7.41)	38.17 (13.37)	< 0.001
Trait anxiety	15.57 (13.20)	39.33 (11.44)	< 0.01
H-R Scale	84.60 (99.41)	114.50 (154.42)	NS
PSS	15 (9.41)	37.50 (4.46)	< 0.001
WHODAS 2.0	13.14 (1.06)	34.75 (8.90)	< 0.001

Hamilton Depression Rating Scale (HDRS), State-Trait Anxiety Inventory (STAI), Holmes-Rahe Social Readjustment Rating Scale (H-R scale), Perceived Stress Scale (PSS), World Health Organization Disability Assessment Schedule (WHODAS 2.0)
NS: non significant

Biomarkers mRNA levels in MDD patients compared with controls

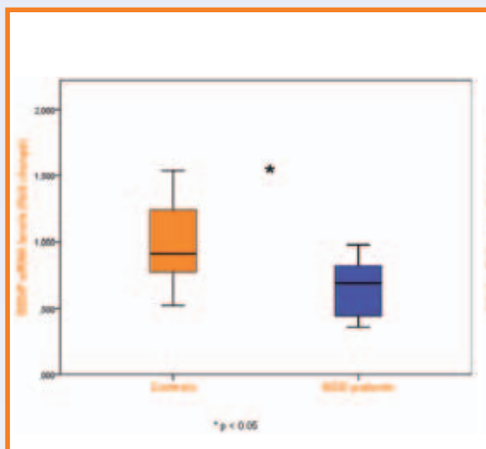


Figure 1: Decreased BDNF mRNA levels in MDD patients compared with control subjects

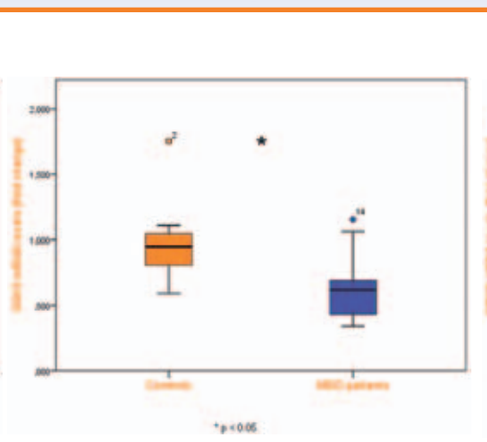


Figure 2: Decreased GSK3 mRNA levels in MDD patients compared with control subjects

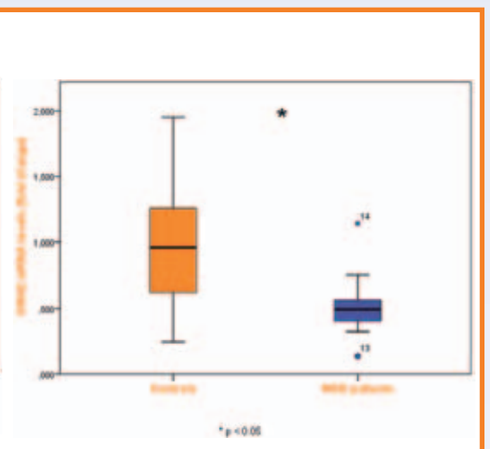


Figure 3: Decreased GRIA2 mRNA levels in MDD patients compared with control subjects

Sex effect on biomarkers levels in MDD patients compared with controls

Fos-B mRNA levels (fold change) were significantly lower in male patients in comparison with female patients ($p < 0.05$) and higher in male patients in comparison with male controls ($p < 0.05$), whereas GSK3 mRNA levels were significantly lower in female patients in comparison with female controls ($p < 0.05$).

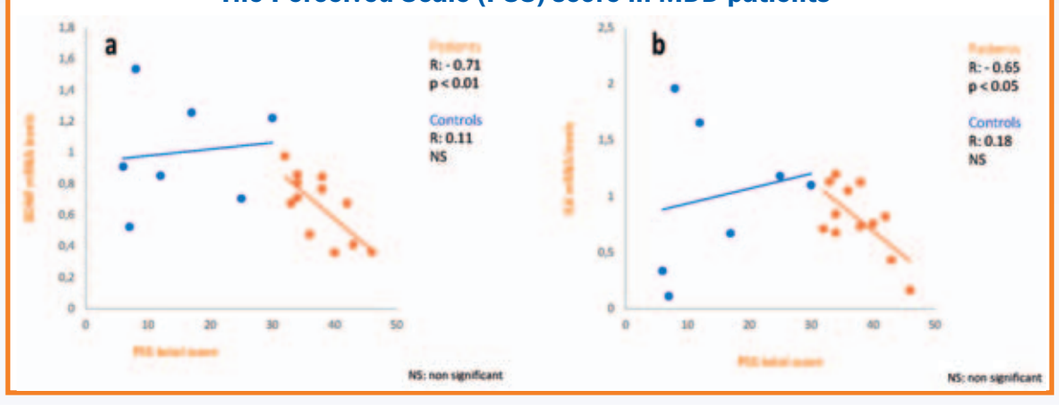
Association between biomarkers levels and demographic and clinical variables (total sample)

BDNF mRNA levels were negatively correlated with the perceived stress (R: -0.54, $p < 0.05$) and the state anxiety scores (R: -0.52, $p < 0.05$).

Association between biomarkers levels and demographic and clinical variables (MDD patients and controls) (figure 4)

Moreover, GRIA2 and IL6 mRNA were positively correlated with age in MDD patients (R: 0.69, $p < 0.05$ and R: 0.71, $p < 0.01$ respectively) but no in controls.

Figure 4: Negative correlation between BDNF (a) and IL6 mRNA levels (b) and The Perceived Scale (PSS) score in MDD patients



Conclusions

These results reveal specific BDNF, GSK3, GRIA2 and Fos-B gene expression changes in ON cells of depressed patients, suggesting that:
(i) these biomarkers of neural plasticity could be relevant as diagnostic tools for MDD
(ii) sex should be taken into account when studying Fos-B and GSK3 expression in ON cells
(iii) the ON is a good cellular model to study the neurobiological mechanisms contributing to mental disorders.

References

[1] Leonard, B.E., 2018. Inflammation and depression: a causal or coincidental link to the pathophysiology? Acta Neuropsychiatrica 30(1), 1-16.
[2] Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., Cui, R., 2017. The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex. Neural Plast., doi: 10.1155/2017/6871089.
[3] Lavoie, J., Gassó Astorga, P., Segal-Gavish, H., Wu, Y.C., Chung, Y., Cascella, N.G., Sawa, A., Ishizuka, K, 2017. The Olfactory Neural Epithelium As a Tool in Neuroscience. Trends Mol Med. 23(2),100-103.

Conflicts of interest: The authors declare no conflict of interest regarding this work.

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