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Brief report

Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system

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ABSTRACT

Despite the evidence of an association between depression and increased inflammatory markers, still little is known in relation to the most severe cases of the disorder i.e., those who fail to respond to antidepressants. We have assessed the cytokine profile and cortisol levels in 21 healthy controls (HC) and 19 medicated patients with depression with treatment-resistance (TRD) moderately ill. As an initial exploratory analysis, we have also related cytokine profile to the patient's clinical treatment outcome after an inpatient admission. Cytokine profile was measured in the serum by the Cytokine Array I kit (Randox®). Plasma cortisol was carried out using a commercially available for the IMMULITE® system. When compared to healthy controls, depressed patients had higher levels of cortisol, IL-6, IL-10, but lower levels of IL-4 and VEGF. Our exploratory analysis showed subjects who did not go on to respond to the inpatient admission treatment package had lower levels of MCP-1, and a trend toward lower levels of VEGF. Taking together, these data suggest that lack of clinical therapeutic benefit of antidepressants is associated with overall activation of the inflammatory system.

1. Introduction

There is now evidence that some patients with major depression (MDD) present inflammatory activation even in the absence of physical illnesses. Meta-analysis studies confirmed the involvement of inflammatory cytokines in MDD patients (Dowlati et al., 2010; Hiles et al., 2012; Howren et al., 2009). The evidence for inflammatory changes in the brain in depression suggests that an increase in inflammation-induced apoptosis, together with a reduction in the synthesis of neurotrophic factors caused by a rise in brain glucocorticoids, may play a role in the pathology of these disorders. If this is the case, it is expected that the more severe cases of depression – those who are resistant to antidepressant treatment – present further inflammatory disturbance.

Fewer studies have attempted understand whether a pattern of cytokines could present a biomarkers of treatment response at baseline. To our knowledge, only two studies so far have investigated cytokine levels in patients who were refractory to antidepressants. O'Brien et al. (2007) showed that antidepressants reduce cytokine levels only in those who respond to antidepressant treatment. Yoshimura et al. (2009) also showed that refractoriness to antidepressant treatment is associated with higher levels of IL-6 levels. Nevertheless, two recent meta-analyses have confirmed the anti-inflammatory role of some classes of antidepressants (Hannestad et al., 2011). They did not, however, characterize treatment-resistant or-responsive patients under a biological perspective. In the present study, we have investigated the cytokine profile of patients with historically defined treatment-resistant major depression. We have also conducted exploratory analysis to understand whether cytokine profile at baseline could vary in relation to treatment outcome.

2. Materials and methods

The study protocol was approved by the Research Ethics Committee of the Institute of Psychiatry, King's College London and Maudsley Hospital (London). All subjects gave their written and informed consent.

Participants: Twenty-one healthy controls were recruited through members of the local community, and free of any self-reported psychiatric illness. Concomitantly, nineteen treatment-resistant depressed (MDD) inpatients were examined one-two weeks after their admission at the National Affective Disorders Unit, Bethlem Royal Hospital, London, UK. Inclusion criteria were: (1) receipt of a

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period of intensive inpatient treatment (rather than assessment); (2) diagnosis of a primary affective disorder; (3) failure to respond to at least one prior adequate medication trial; and (4) HRSD score of ≥ 16 on admission. At admission, all patients underwent intensive psychopharmacology in-patient treatment using combinations of medications as indicated by the Maudsley prescribing guidelines (Taylor et al., 2007). Detailed evaluation of this specialist inpatient treatment for refractory affective disorder unit is extensively described (Wooderson et al., 2011). Some of these patients have been used on a previous study in treatment-resistance patients (Carvalho et al., 2008).

Clinical assessment: Diagnoses were made according to the 10th revision of the International Classification of Diseases (ICD-10) (World Health Organisation, 1992) and use of the SCID-II (Structured Clinical Interview for DSM-IV, version II). Exclusion criteria for participants were: history of hypersensitivity to corticosteroids or steroid use; heavy smokers (i.e., more than 20 cigarettes/day); drugs known to modify immune and endocrine functions for at least one month before blood sampling, including oral contraceptives, pregnant/lactating women; alcohol dependence; and significant physical illnesses. Healthy controls were further excluded if they used any psychotropic medications. For ethical reasons, it was not possible to withdraw antidepressants and assess the patients in a drug free state; however, a switch in medication was avoided for at least 14 days before experimental procedures.

Treatment-resistance: Further measures of treatment-resistance involved historical assessment by Sackeim's definition, whereby resistance to a given treatment is concluded if, despite continued adherence to the same medication and dosage that produced an initial response, a patient experienced relapse or recurrence of a depressive episode (Sackeim, 2001). We also used Thase and Rush (1997) staging criteria, which recognises five stages of treatment-resistance according to the number of treatment trials adequately delivered.

Clinical severity: Depression severity was examined using the 21-item Hamilton rating scale (HAM-D, Hamilton, 1960) and Beck depression inventory (BDI) at admission and discharge. To check for other symptoms we used: anxiety, Beck anxiety inventory (BAI) (Beck et al., 1988), suicide ideation, BECK Suicide Ideation (BSI), Beck et al., 1979), hopelessness, Beck hopelessness scale (BHS), Beck et al., 1974), and recent life events, recent life events questionnaire (RLCQ), Casey et al., 1967) at admission. Pharmacological response to treatment was defined using the a priori definition of a reduction in HAM-D score of 50% or greater.

Sample measurements were conducted with commercially available kits according to manufacturer's protocol: Serum multiplex cytokine was analysed by (Randox Laboratories Ltd) and plasma cortisol by IMMULITE® (Diagnostics Products Corporation, Los Angeles, CA). For cortisol: CV values—7.1% within run, 7.8% between runs, detection limit 5.5 nmol/L.

2.1. Statistical analysis

Two groups were compared for continuous variables by Mann–Whitney, and for discrete variables by the Chi-Square test. Since the majority of the cytokines, checked by the Kolmogorov–Smirnov test, were not normally distributed and transformations did not improve linearity non-parametric tests were used. We conducted two subsequent analyses. First, we compared controls versus all depressed patients. Second, as exploratory analysis we compared responsive versus refractory patients to antidepressant treatment. Results are expressed as median q25–q75 of raw cytokine levels. Raw values of cytokines were correlated with scale scores using the Spearman's coefficient. Multiple testing corrections were applied via the method of Simes' for correlated parameters (Rødland, 2006). The significance level was set to $p \leq 0.05$ (two-tailed) and computer statistical

Table 1
Socio-demographic and clinical characteristics of the treatment-resistant depressed who responded (MDD R) or not (MDD NR) to pharmacological treatment, and healthy controls. Percentages are given in brackets.

Parameters	MDD R	MDD NR	Healthy controls	*p*-value
N	6	13	21	–
Sex (M/F)	3/3	03/11	06/15	0.275
Age (AVG ± SEM)	47.2 ± 3.0	50.9 ± 3.6	45.9 ± 2.4	F=1.03, 0.314
BMI (AVG ± SEM)	29.1 ± 2.6	28.80 ± 1.1	28.90 ± 0.99	F=0.02, 0.889
BDI	32.7 ± 3.7	37.6 ± 3.6	2.1 ± 0.6	F=214.4, 0.001
HAM-D admission	21.8 ± 1.9	21.7 ± 2.1	–	0.767
HAM-D discharge	6.0 ± 2.5	13.4 ± 4.3	–	0.002
BHS	13.2 ± 2.2	15.7 ± 1.2	–	0.239
BAI	14.3 ± 4.7	25.1 ± 3.7	–	0.080
RLCQ	413.0 ± 150.1	334.6 ± 48.9	–	0.535
BSI	14.33 ± 3.0	20.0 ± 2.8	–	0.183
Duration of current episode (years)	3.3 ± 1.2	6.3 ± 1.8	–	0.259
Number previous hospital admissions	5.2 ± 1.3	4.4 ± 1.0	Drug free	0.689
Current medications	1 Drug free	6 Drug free	–	–
	4 Mood stabilizers	5 Mood stabilizers	–	–
	5 SSRI/SNRI	8 SSRI/SNRI	–	–
	1 Benzodiazepines	3 Benzodiazepines	–	–
	2 Atypical antipsychotics	1 Atypical antipsychotics	–	–
	1 Tri/tetracyclic	4 Tri/tetracyclic	–	–
	2 MAOI	1 MAOI	–	–
	Other antipsychotics	1 Other antipsychotics	–	–
	Non psychotropics	2 Non psychotropics	–	–
ECT in the past	4/6	10/13	–	0.517
Treatment-resistant stage: *n* (%)			–	0.665
Stage 4+failure to respond to ECT:	70%	70%	–	–
Stage 3+no response to 2nd augmentation	30%	20%	–	–
Stage 2+no response to 1st augmentation	00%	10%	–	–

AVG—average, F—female, BMI—body mass index, ECT—eletroconvulsotherapy, Treatment Resistance Stage—Thase and Rush treatment resistance criteria, MAOI—monoamine oxidase inhibitor, SSRI—selective serotonin reuptake inhibitor, SNRI—selective noradrenaline reuptake inhibitor, M—males, BHS—Beck hopelessness scale, BAI—Beck Anxiety Inventory, RLCQ—recent life changes questionnaire, BSI—Beck Suicide Scale, HAM-D—Hamilton depression scale, MDD R—treatment responsive, MDD NR—treatment non responsive, SEM—standard error of the mean.