Journal of Psychiatric Research 105 (2018) 17–22

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Genetic disposition to inflammation and response to antidepressants in major depressive disorder

Alyson Zwicker[a,b,c], Chiara Fabbri[d,e], Marcella Rietschel[f], Joanna Hauser[g], Ole Mors[h], Wolfgang Maier[i], Astrid Zobel[i], Anne Farmer[d], Katherine J. Aitchison[j], Peter McGuffin[d], Cathryn M. Lewis[d], Rudolf Uher[a,b,c,d,*]

[a] Department of Pathology, Dalhousie University, Halifax, NS, Canada
[b] Department of Psychiatry, Dalhousie University, Halifax, NS, Canada
[c] Nova Scotia Health Authority, Halifax, NS, Canada
[d] King's College London, Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, UK
[e] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[f] Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[g] Laboratory of Psychiatric Genetics, Department of Psychiatry, Poznan University of Medical Sciences, Poland
[h] Aarhus University Hospital, Risskov, Psychosis Research Unit, Aarhus, Denmark
[i] Department of Psychiatry, University of Bonn, Bonn, Germany
[j] Department of Family Medicine, University of Alberta, Edmonton, AB, Canada

ARTICLE INFO

Keywords:
Major depressive disorder
Antidepressant efficacy
Inflammation
C-reactive protein
Polygenic risk score

ABSTRACT

Background: Inflammation may play an important role in depression and its treatment. A previous study found that increased C-reactive protein (CRP), a marker of systemic inflammation, is associated with worse response to the serotonergic antidepressant escitalopram and better response to the noradrenergic antidepressant nortriptyline. It is unclear whether this reflects genetic disposition to inflammation.
Methods: We analyzed genotype data and weekly Montgomery-Åsberg Depression Rating Scale scores (MADRS) from 755 unrelated individuals obtained over a 12-week period in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. We calculated a polygenic risk score for CRP level based on genome-wide meta-analysis results from the CHARGE Consortium.
Results: A higher polygenic risk score for CRP was associated with slightly better response to escitalopram and slightly worse response to nortriptyline, reflected in a statistically significant interaction between polygenic risk score and drug (beta = 1.07, 95% CI = 0.26–1.87, p = 0.0093).
Discussion: A differential association between CRP-PRS and antidepressant drug that is in a direction opposite to that found with serum CRP measurement suggests that previously observed effect of inflammation on antidepressant efficacy may be driven by state factors distinct from genetic influences on systemic inflammation.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric illness associated with substantial personal and socioeconomic burden. It affects more than 350 million individuals worldwide and it is a leading cause of disability (WHO, 2012). MDD is typically treated with antidepressants. However, less than 50% of individuals diagnosed with depression achieve satisfactory improvement following treatment with their first antidepressant (Trivedi et al., 2006). The current trial-and-error approach to treating depression is difficult for patients and often delays recovery (Steimer et al., 2001). Even after multiple attempts at pharmacological treatment of depression, approximately one third of individuals do not respond to conventional antidepressants (Rush et al., 2006). Therefore, there is a pressing need to identify reliable predictors to indicate which individuals will likely respond better to one antidepressant over another.

The immune system, and specifically the inflammatory response, has been implicated in depression and its pharmacological treatment. Psychosocial stress elicits an immune response, resulting in inflammation (Bierhaus et al., 2003). Elevated inflammation following an exposure to a stressor increases the likelihood of developing depression (Aschbacher et al., 2012). Increased serum concentration of an

* Corresponding author. Department of Psychiatry, Dalhousie University, Halifax, NS, Canada.
E-mail address: uher@dal.ca (R. Uher).

https://doi.org/10.1016/j.jpsychires.2018.08.011
Received 19 February 2018; Received in revised form 11 June 2018; Accepted 2 August 2018

inflammatory biomarker has also been shown to predict more severe symptoms among those with MDD (Köhler-Forsberg et al., 2017). Additionally, individuals who have experienced early life stressors that are associated with later development of depression, such as childhood maltreatment, show increased inflammatory responses to lab stressors and increased levels of inflammation in adulthood (Baumeister et al., 2016; Nanni et al., 2012; Pace et al., 2006). Importantly, higher levels of systemic inflammation may also be associated with inadequate response to pharmacological treatments (Strawbridge et al., 2015).

C-reactive protein (CRP) is a reliable marker of systemic inflammation and it is readily testable in most medical laboratories (Miller et al., 2009). It has been demonstrated that CRP level can differentially predict who will respond better to two antidepressants with distinct mechanisms of action. Individuals with low baseline CRP levels (< 1 mg/L) have been shown to respond better to the serotonergic antidepressant escitalopram and individuals with higher baseline CRP respond better to the noradrenergic antidepressant nortriptyline (Uher et al., 2014). CRP and its interaction with drug explained more than 10% of the individual-level variance in treatment outcome (Uher et al., 2014). This finding has been partially replicated in an independent sample of MDD patients, where individuals with high serum CRP (> 1 mg/L) showed lower rates of remission with escitalopram monotherapy than those with lower serum CRP levels (Jha et al., 2017). However, single measurements of CRP can be easily perturbed by state factors such as recent infections, injuries, body mass index (BMI), or inflammatory conditions (Kathiresan et al., 2006). Additionally, the effects of some genetic variants on levels of CRP may be conditional on BMI (Dehghan et al., 2011). It is therefore desirable to examine more stable indicators of propensity to systemic inflammation.

Genetic factors likely influence both serum CRP levels and response to antidepressants (Tansey et al., 2013). It has been shown that serum CRP is approximately 50% heritable and specific genetic variants associated with serum CRP have been identified (Dehghan et al., 2011; Sas et al., 2017). Polygenic risk scores (PRS) allow us to test the aggregate effects of hundreds to thousands of variants across the genome on a given phenotype. Using this methodology, it is possible to index an individual's genetic liability to systemic inflammation. The aim of the present study was to test if a polygenic risk score for CRP predicts response to escitalopram and nortriptyline in the same direction as serum CRP levels. We calculated polygenic risk score (CRP-PRS) for escitalopram- and nortriptyline-treated individuals based on the CHARGE consortium genome-wide meta-analysis of CRP levels (Dehghan et al., 2011). Participants who were treated with either drug with both weekly depression symptom ratings and genotype data were drawn from the Genome-based Therapeutic Drugs for Depression (GENDEP) study (Uher et al., 2010). We hypothesized that individuals with a lower CRP-PRS would show better response to escitalopram and that individuals with a higher CRP-PRS would show better response to nortriptyline.

2. Methods

2.1. Target sample

2.1.1. Sample description

The target sample was composed of 755 unrelated individuals from the Genome-based Therapeutic Drugs for Depression (GENDEP) project with genome-wide SNP data and Montgomery-Åsberg Rating Scale for Depression (MADRS) scores. Participant characteristics are shown in Table 1. The GENDEP project is a multi-centre partially randomized clinical and pharmacogenetic study including 811 treatment-seeking individuals diagnosed with unipolar depression of at least moderate severity according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) or ICD-10 (International Classification of Diseases, 10th revision) criteria, established using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) semi-structured interview. Participants ranged in age from 19 to 72 years and were of Caucasian European ancestry. Exclusion criteria were a family history of bipolar disorder in first-degree relatives, lifetime personal history of schizophrenia or bipolar disorder, current substance dependence, and pregnancy (Uher et al., 2010). Participants were allocated to receive treatment with one of two antidepressant drugs: nortriptyline (50–150 mg daily) or escitalopram (10–30 mg daily). Participants with no contraindications were randomly allocated to receive either nortriptyline or escitalopram. Participants with contraindications for one antidepressant were non-randomly allocated to the other drug. The present study includes 432 participants treated with escitalopram and 323 participants treated with nortriptyline with both genotype data and weekly MADRS scores. The GENDEP project was approved by ethics boards of participating centers, and all participants provided written informed consent.

Table 1
Participant characteristics.

	Treatment Arm	
	Escitalopram *n = 432*	**Nortriptyline** *n = 323*
Randomized, *n (%)*	226 (52.3)	222 (68.7)
Female, *n (%)*	269 (62.3)	203 (62.9)
Age in years, *mean (SD)*	*42.2 (11.5)*	*42.2 (11.6)*
Baseline MADRS, *mean (SD)*	28.5 (6.6)	29.4 (6.8)
MADRS change, % (SD)	54.7 (32.1)	49.3 (32.8)

MADRS change = change in MADRS score from baseline to week 12.

2.1.2. Antidepressant response

The outcome measure of the present study was total score on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979), administered weekly for 12 weeks by trained psychiatrists and psychologists with high interrater reliability (Uher et al., 2012, 2008).

2.1.3. Genotyping, quality control, and imputation

We genotyped 550,337 single nucleotide polymorphisms (SNPs) with Illumina Human610-quad chip in DNA extracted from peripheral blood samples obtained at baseline (Uher et al., 2010). Additional genotyping was performed using the Illumina Infinium Exome-24 v1.0 BeadChip that includes ~250 K coding variants. We completed pre-imputation quality control on genome-wide and exome array data by excluding variants and participants according to the following criteria: 1) variants with missing rate ≥5%; 2) monomorphic variants; 3) participants with genotyping rate < 97%; 4) participants with sex discrepancies between self-reported sex and genetic sex; 5) participants with abnormal heterozygosity; 6) related participants (identity by descent (IBD) > 0.1875) (Anderson et al., 2010); 7) population outliers according to Eigensoft analysis of linkage-disequilibrium-pruned genetic data (Patterson et al., 2006; Price et al., 2006); and 8) GWAS discordant participants (for exome data only). Hardy–Weinberg equilibrium was tested, but was not used as an exclusion criterion for markers because departures from Hardy–Weinberg equilibrium are expected in a case-only study (Wittke-Thompson et al., 2005).

Data were imputed using Minimac3 via the Michigan Imputation Server (https://imputationserver.sph.umich.edu/start.html). Post-imputation quality control consisted of pruning variants with poor imputation quality (R^2 score < 0.30) (Li et al., 2010; Pistis et al., 2015) or minor allele frequency (MAF) < 0.01.

2.2. Polygenic risk scores

2.2.1. Reference sample for polygenic risk score derivation

We constructed the CRP-PRS based on the results from the CHARGE Consortium meta-analysis of genome-wide association data for CRP levels (Dehghan et al., 2011). It has been demonstrated that a genetic