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ScienceDirect
Psychiatry Research 145 (2006) 61 – 65
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Pooling pharmacogenetic studies on the serotonin transporter: A mega-analysis

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Received 22 January 2004; received in revised form 28 August 2005; accepted 17 September 2005

Abstract

Pharmacogenetic studies on antidepressants have reported an association between the promoter of the serotonin transporter gene (SERTPR) and response to antidepressant treatment. In the present study, individual subject data from three pharmacogenetic studies on SERTPR were pooled ('mega-analysis') to investigate the role of this gene in the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs). A group of 548 patients who were treated with different SSRIs in a double blind design were included; the severity of depressive symptoms was weekly assessed with the Hamilton Rating Scale for Depression. SERPR allelic variants were determined in each subject using a PCR-based technique. In the whole sample, subjects with SERPR* l/l variants showed a significantly better response to treatment, and this effect was independent from analyzed demographic and clinical variables but was not uniform across samples. This result supports the involvement of the SERTPR gene in response to antidepressant treatments.

Keywords: Pharmacogenetics; Mood disorders; Antidepressant treatment

1. Introduction

The serotonin pathway has been widely investigated for its possible involvement in the pathogenesis of depression and sertoninergic mechanisms that are thought to be implicated in antidepressants action. In particular the serotonin transporter (SERT), which is thought to be one of the most important sites of binding for antidepressants, has been widely investigated for its possible role as a biological marker for antidepressants response. In 1996 Lesch et al. (1996) reported that the transcriptional activity of the long (l) variant in the promoter of the gene, called the SERT-gene-linked polymorphic region (SERTPR), is more than twice as active as the short (s) variant; therefore it has been hypothesized that inter-individual variations in response to antidepressant treatment are related to genetic differences at the SERTPR level. A positive association between the long allele on SERTPR and a better response to selective serotonin reuptake inhibitors (SSRI) was detected and replicated in a number of studies (Perlis et al., 2003; Pollock et al., 2000; Smeraldi et al., 1998; Zanardi et al., 2000, 2001), although conflicting findings have been reported in Asian

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0165-1781/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2005.09.020

populations (Kim et al., 2000; Yoshida et al., 2002; Yu et al., 2002). This result seems to be limited to subjects affected by mood disorder, while for patients with other psychiatric diagnoses, treated with success with the same drugs, the results are uncertain (Billett et al., 1997; Rausch et al., 2002a).

When investigating genetics of a complex trait, such as drug response, the influence of a single gene is likely to be modest and very large samples are necessary; moreover, a different effect in subgroups could be missed. A meta-analytic approach may enhance the ability to investigate pharmacological response, by increasing sample size and statistical power; however, the variability in study designs, or insufficient adjustment for confounders, could hamper the detection of relevant results. An alternative strategy is the use of the raw information from individual subjects, so-called 'mega-analysis', allowing one to pool the original data and to re-analyze them for differences among subgroups (DeRubeis et al., 1999; Thase et al., 1997).

Therefore, to investigate the possible influence of the SERTPR polymorphism on antidepressant response to SSRIs, individual subject data from pharmacogenetic studies were pooled in the present study to perform a mega-analysis (Minov et al., 2001; Rausch et al., 2002b; Serretti et al., 2003) (the last sample was previously analyzed for the G-beta3 subunit; the same subjects have been partially published in a series of articles (Smeraldi et al., 1998; Zanardi et al., 2000, 2001; Serretti et al., 2004). The three studies were performed in different settings (i.e. in- and out-patients); therefore, the subjects were likely to be different, i.e. for age distribution, symptomatology and number of previous episodes; our a priori hypothesis was that the effect of the genotype on pharmacological response would not differ across groups of patients recruited in different studies; we therefore decided to include all subjects for whom we had information about pharmacological response in our mega-analysis.

2. Methods

2.1. Sample

We contacted all of the primary investigators who had published, or presented data on SERTPR and antidepressant response in mood disorders up to early 2003, and we asked them to participate to our mega-analysis; we were able to collect individual data from three centers.

All subjects were recruited in psychiatric units, and were determined to have a Major Depressive Episode (DSM-IV criteria). In the sample of Minov et al., only 44 patients out of 173 could be included because they were treated with SSRI (paroxetine), while the others were treated with different therapies (mirtazapine, tricyclics, electroconvulsive therapy); we included the 51 patients from Rausch et al. who were treated with fluoxetine and 487 subjects out of 490 ($n=351$ treated with fluvoxamine and $n=136$ with paroxetine) from Serretti et al. (2003) (three subjects were excluded because of genotyping problems) previously published in various reports (Smeraldi et al., 1998; Zanardi et al., 2000, 2001) plus a manuscript submitted. All the subjects were genotyped for SERTPR variants with the same methodology (see Lesch et al., 1993) and all were evaluated with Hamilton Depression scale during antidepressant treatment. Therefore we analyzed the clinical and demographical variables in a total sample of (44+51+487) 582 subjects.

To analyze genotypes and response to SSRI treatment in a more homogenous sample, the pharmacogenetic analysis was performed with consideration of possible confounding factors: five subjects of non-Caucasian origin were excluded, as well as seven Caucasian subjects from the Rausch et al. study who were treated with placebo through the 6-week mega-analysis endpoint, three subjects for whom the diagnosis was not Major Depressive Episode (dysthymia), and one for dropout (manic switch).

Another major issue was how to adjust consistently for the drug dosage; all the subjects followed in the Departments of Psychiatry of Milan and Munich have been treated with "therapeutic" dosages of antidepressants ($\geq$10 mg paroxetine or fluoxetine; $\geq$50 mg fluvoxamine), whereas 19 subjects from the Rausch study were randomized to initially receive less than 5 mg of fluoxetine through the 6th week for its pharmacogenetic dose–response design. Those subjects were excluded for the mega-analysis purposes; finally for four subjects starting at 6th week with 5 mg of fluoxetine, we decided to consider as baseline the depress score at the week in which the threshold value of 5 mg/day was reached.

As a secondary analysis, given the differences among groups, for example, in clinical features (Bipolar Disorder diagnosis and presence of psychotic features) and the presence of augmenting therapy (pindolol) in the Italian sample, we excluded from the Milan sample those subjects affected by Bipolar Disorder, with psychotic features or treated with pindolol as augmentation.

2.2. Methods of mega-analysis

The main outcome measure was the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967),