Research Article

Exploring Gene-Treatment Interactions: Dissociated Effect of COMT Val108/158Met Genotype on Negative Symptoms Response to Haloperidol and Risperidone Vs Clozapine

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Abstract

Aims: this study aims to evaluate the effect of COMT rs 4680 (Val108/158Met) polymorphism, known to regulate dopamine levels, on specific response pattern to antipsychotics characterized by different dopaminergic activity.

Materials and Methods: the sample included 153 subjects diagnosed with schizophrenia, treated either with haloperidol, risperidone or clozapine. Clinical evaluation with PANSS scale was assessed at the beginning of treatment and at week eight. All patients underwent genetic analysis for the polymorphism of interest.

Results: at week 8 we found a significant genotype-treatment interaction for PANSS Negative subscale variation. Among patients on haloperidol and risperidone, the improvement was greater for carriers of Met allele, while in the clozapine group a greater improvement was observed for Val/Val genotype.

Conclusions: our results, although preliminary, suggest that COMT Val/Val genotype could represent a biological marker for treatment with clozapine in subjects with prominent negative features.

Keywords: Schizophrenia and psychosis; Genetics; Psychopharmacogenetics; Antipsychotics, Clozapine.

1. Introduction

Schizophrenia is a major focus of research in psychiatry, since it is a severe and common disorder and treatment outcomes are still unsatisfactory. First generation antipsychotics have well-known extrapyramidal side effects, and second-generation drugs have equally concerning metabolic complication. Moreover, patients often show incomplete clinical response or do not respond at all to antipsychotic treatment (Foster, Miller & Buckley, 2007). In particular, negative features are likely to persist in patients with chronic schizophrenia, despite antipsychotic treatments, thus contributing to long-term disability (Chue & Lalonde, 2014) Genetic factors may

contribute to the inter-individual variability in response to drug treatment, specifically to some symptom clusters. Among these, the Cathecol-O-methyltransferase (COMT) gene has long been considered a candidate for psychosis, not only because it encodes a key dopamine catabolic enzyme, but also maps on the Velo-Cardio-Facial syndrome region on chromosome 22q11 (Armando, Papaleo & Vicari, 2012), a disorder associated with increased risk for psychosis. A nonsynonymous polymorphism (Val108/158Met), rs 4680, at the COMT locus has been shown to affect the function of the encoded enzyme, the Val allele conferring increased activity and thermostability (Lotta et al., 1995). The putative association between COMT polymorphism and schizophrenia has been described as promising (Shifman et al., 2002, Voisey et al., 2012), but many studies have produced negative results (Tovilla-Zarate et al., 2013, Zhang et al., 2012, Lajin et al., 2011).

The most consistent results report an association between COMT Met allele, characterized by lower enzymatic activity and therefore higher DA levels (Winterer & Weinberger, 2004), and more efficient Prefrontal Cortex (PFC) activation and related cognitive performances (Egan et al., 2001, Lopez-Garcia et al., 2012, Ceaser, Csernansky & Barch, 2013). Moreover the COMT genotype seems to influence outcomes of neuroremediation protocols, also in interaction with pharmacological treatment (Bosia et al., 2007, Panizzutti, Hamilton & Vinogradov, 2013, Bosia et al., 2014). Regarding clinical features, it has been reported an association between the Val allele and more prominent negative symptoms (Pelayo-Teran et al., 2008, Li et al., 2012), however other studies found negative results (Tovilla-Zarate et al., 2013).

Several studies also explored the effect of Val108/158Met polymorphism on clinical response to pharmacological treatments. Based on observations that second-

generation antipsychotics may improve neuropsychological performances in some patients (Weickert et al., 2004), possibly via increasing prefrontal dopamine Gessa et al., 2000), some studies focused on cognitive improvements, reporting significant effects of COMT genotype and interactions with treatments on several domains (Weickert et al., 2004, Bertolino et al., 2004, Woodward, Jayathilake & Meltzer, 2007). Addressing more specifically to clinical response, Molero et al. (2007) observed higher severity of psychotic symptoms and a worse response to treatment in patients homozygous for the Val allele (Molero et al., 2007), a result supported by findings of an overrepresentation of the Val allele among poor responders to risperidone (Gupta et al., 2009) and of a better response among Val/Met subjects (Gao et al., 2012). However other studies suggested a correlation between Met allele and both poor response to typical antipsychotics (Anttila et al., 2004, Inada, Nakamura & Iijima, 2003, Hagen et al., 2008) and higher daily dosages (Hagen et al. 2008). Still, lack of association between COMT genotype and response to antipsychotic treatment has been reported (Illi et al., 2007, Tybura et al., 2012, Vehof et al., 2012). Therefore results are so far inconsistent, probably also because of heterogeneity of the samples studied and variability of the assessments employed.

Given the effects of COMT genotype on the dopaminergic system, specifically in the PFC it is worth to better analyze specific interactions with different antipsychotic classes, characterized by a different activity at dopaminergic transmission level, on dimensional response profile. We hypothesized that COMT Val108/158Met polymorphism, could differentially influence response to haloperidol, risperidone and clozapine and that the effect could be greater on negative symptoms, as they are more dependent on PFC dopamine levels. Haloperidol, risperidone and clozapine are

characterized by progressively lower ratio of dopaminergic D2 receptor blockade activity and known to be a useful clinical tool in a sequential approach to discriminate between heterogeneous schizophrenia subpopulations and narrow the pharmacological response prediction (Cavallaro, Brambilla & Smeraldi, 1998). We specifically included clozapine, the gold standard of treatment-resistant schizophrenia, because of its peculiar role in dopaminergic system and the interest in exploring possible predictors of response that could represent markers for direct clozapine treatment.

2. Materials and Methods

2.1 Sample

The sample included 153 biologically unrelated subjects (100 males and 53 females), recruited from Italian patients followed by the Psychotic Disorders Centre of the Department of Clinical Neurosciences, IRCCS San Raffaele in Milan. To be included, patients had to:

1. meet DSM-IV diagnostic criteria for schizophrenia;
2. be older than 18 years and younger than 65;
3. be eligible for antipsychotic monotherapy with haloperidol, risperidone or clozapine;
4. show no evidence of substance dependence or abuse, co-morbid diagnosis on Axis I or II, epilepsy, or any other major neurological illness or perinatal trauma, or mental retardation.

Informed consent to participate in the study (including genetic analysis and use of clinical data) was obtained from all patients. The protocol and informed consent

followed the principles of the Declaration of Helsinki; furthermore it was accepted and approved by the local Ethical Committee.

2.2 Clinical Assessment

Subjects were treated with haloperidol, risperidone or clozapine, introduced in a sequential order for indication of resistance and/or intolerance to neuroleptics (in the case of risperidone), or to both neuroleptics and at least one second generation antipsychotic, in the case of clozapine (Cavallaro, Brambilla & Smeraldi, 1998). All patients treated with haloperidol, except two, were drug-naive.

Basic information, such as age, sex, education, duration of illness and medication history, psychopathological measures were collected from clinical interviews and records.

Psychopathology was assessed by means of the Positive and Negative Symptoms Scale for Schizophrenia (PANSS) (Kay, Fiszbein & Opler, 1987), at first administration of the antipsychotic and after 8 weeks of treatment. Baseline and post-treatment PANSS were administered by the psychiatrist who was in charge of the patient, blind to genotype. All the psychiatrists (4) who did the assessments have previously been trained on PANSS rating and calibration.

2.3 DNA analysis

All patients underwent a venous blood sample for genotypic analysis. Genomic DNA was extracted using EXTRAGEN 8C. PCR was performed with the following primers: 5’ ACT GTG GCT ACT CAG CTG TG 3', 5' CCT TTT TCC AGG TCT GAC AA 3'. PCR product was digested using NlaIII (New England Biolabs,

England, UK); fragments were separated in 3% Seakem agarose gels (BMA, BioWhittaker Molecular Applications. Rockland, ME - USA). The cleaved bands were visualized by ultraviolet light. Depending on the presence of one or two restriction NlaIII sites, either two fragments 140bp+29bp (allele G or Val) or three fragments 114bp+26bp+29bp (allele A or Met) were produced (Lachman et al., 1996).

2.4 ***Data analysis***

A Hardy-Weinberg equilibrium was assessed for genotypes.

For genetic analysis, we grouped patients as COMT Val/Val and Met carriers as in our previous work (Bosia et al., 2007).

Demographic and clinical characteristics at baseline were compared using analysis of variance (ANOVA), or chi-squared tests when appropriate.

The effect of antipsychotic treatments and genotype on psychopathological features was analyzed by means of Repeated Measures ANOVA, with PANSS Total score, Positive, Negative and General subscales, at enrolment and at week 8, as dependent measures, antipsychotic treatment and COMT genotype as categorical predictors and Time as fixed variable. Bonferroni's correction for multiple tests was applied, thus the value of p less than 0.013 was considered significant.

To interpret the interaction between genotype and treatment on the improvement in the PANSS Negative Symptoms Subscale, we divided the sample into two subgroups according to pharmacological treatment. Because of the small sample size and based on their D2 receptorial affinity, we grouped patients taking haloperidol and risperidone, as in previous studies (Nolan et al., 2006). We then evaluate the

effect of genotype on improvement in PANSS Negative Symptoms Subscale in each treatment group by means of analysis of covariance (ANCOVA), with PANSS Negative Symptoms' change scores corrected for baseline as dependent variable, COMT genotype as categorical factor and age and drug dosage as covariates.

Analysis were performed using STATISTICA software version 8.

3. Results

3.1 Descriptive analysis

DNA analysis showed an allelic distribution according to Hardy-Weinberg equilibrium for COMT genotype: 47 patients Val/Val, 72 Val/Met and 34 Met/Met. 19 patients were treated with haloperidol (3 Val/Val, 13 Val/Met and 3 Met/Met), 40 with risperidone (14 Val/Val, 16 Val/Met and 10 Met/Met), 94 with clozapine (30 Val/Val, 43 Val/Met and 21 Met/Met). The mean dose (mg/day) was 4.39+/-2.06 for haloperidol, 3.16+/-1.46 for risperidone and 244.30+/-101.00 for clozapine.

Baseline characteristics of each treatment group are shown in Table 1.

A Chi-Square analysis didn't show a significant difference in frequencies of genotypes in the three treatment groups (Chi square =2.4 d.f.=2; p= .30). A one-way ANOVA didn't show any significant effect of genotype on daily dosage for any of the three antipsychotics used.

The ANOVA for the demographic and clinical characteristics and baseline PANSS Total, Positive, Negative and General scores didn't show any significant interaction between genotype and antipsychotic treatment.

3.2 ***Clinical response analysis***

The repeated measures ANOVA showed a significant effect of Time for PANSS Total scores and each subscale, Positive, Negative and General (p<.000 for all), no

significant main effects of treatment and genotype. The mean percentage change in symptoms rating is reported in Table 2.

A significant treatment by genotype interaction was found only for the PANSS Negative Symptoms Subscale scores (df=2;F= 6.05; p=.003). In the subgroup treated with clozapine, the ANCOVA showed a significant effect of COMT genotype on PANSS Negative Symptoms change score (df=1; F=8.94;p=.004), with greater improvement among Val/Val patients, as shown in Fig.1. No significant effect was observed for the covariates (F=.53;p=.47 for age and F=.13;p=.72 for drug dosage).

Among patients treated with haloperidol or risperidone, the ANCOVA showed a significant effect COMT genotype on PANSS Negative Symptoms change score (df=1; F=5.21;p=.026), with greater improvement among Met carriers, as shown in Fig.2. No significant effect was observed for the covariates (F=1.10;p=.30 for age and F=.30;p=.87 for drug dosage).

4. Discussion

At basal evaluation we didn't find any difference between COMT genotype groups for clinical-demographic characteristics and psychopathological assessments. This finding supports previous studies reporting negative association between COMT Val/Met polymorphism and clinical features (Tovilla-Zarate et al., 2013), suggesting that the specific effect of COMT gene is likely to be very small, and could differentially influence clinical symptomatology strongly depending on other underlying genetic factors. Moreover we didn't observe any association between COMT genotype and mean antipsychotic daily dosage, as previously reported (Illi et al., 2007).

After 8 weeks of treatment we observed a global improvement in all psychopathological dimensions, without significant differences between treatment and genotype groups, except for negative symptoms. The absence of significant between-groups differences for the change in PANSS Total scores and the Positive subscale may be secondary to the use of a sequential approach to treatment, with haloperidol introduced at first and then switched to risperidone and last to clozapine if the patient does not respond or is intolerant to previous treatment. Following this approach, the observed response allows to identify more homogenous subpopulation of patients, each possibly characterized by a more homogeneous set of underlying genetic factors. In this view it is likely that the three groups naturalistically selected on the basis of pharmacological response may show a similar global clinical improvement and positive symptoms reduction. Also regarding the PANSS General subscale we didn't find any differences in change between groups and this was again rather expected, given that the General subscale includes a variety of aspecific symptoms less related to the "core" of schizophrenia.

Regarding negative symptoms, we found a significant interaction of treatment by genotype on improvement at 8 weeks. We observed a dissociated effect of COMT Val108/158Met genotype on negative symptoms response to haloperidol and risperidone vs clozapine. Among patients treated with haloperidol or risperidone, the analysis showed a significantly greater PANSS negative subscale improvement in subjects carrying the Met allele. In the subgroup treated with clozapine, on the contrary, a higher negative symptoms change was observed among Val/Val homozygous. These results show that the COMT Val/Met polymorphism differentially influences changes in negative symptoms, independently of baseline

scores, after 2 months of treatment with different antipsychotics. Negative features represent one of the core domains of schizophrenia, predictor of poor functional outcome and still poorly responsive to antipsychotic therapies (Lindenmayer et al., 2004). Negative features represent one of the core domains of schizophrenia. On the one hand, negative symptoms have been associated to poor functional outcome. On the other hand, the effect of currently available antipsychotics on negative symptoms is still unsatisfactory (Lindenmayer et al., 2004). Negative symptomatology has been associated to reduced prefrontal cortex activity (Itoh et al., 2011) and worse related performances, such as executive functions (Bagney et al., 2013), suggesting a critical role for prefrontal dopaminergic transmission. According to these data, among psychopathological dimensions of schizophrenia, negative features appear the most likely to be modulated by the COMT Val/Met functional polymorphism. Our result suggests that the COMT polymorphism could interact with different antipsychotic treatments resulting in opposite trends on negative symptoms results, depending on the antidopaminergic activity of the compound. Specifically we observed that subjects carrying the Val allele in homozygosis present a significant reduction of negative symptoms only when treated with clozapine, whereas the degree of improvement is minimal when treated with haloperidol or risperidone, drugs characterized by higher dopaminergic blockade. The mechanism contributing to the observed effect is still largely unknown and it is unlikely to be related specifically only to the COMT polymorphism. However there are some findings that lead to possible speculations on results interpretation. Slifstein et al. (2008) reported an association between COMT Val/Met polymorphism and prefrontal availability of D1 receptors, the

Val/Val genotype leading to higher D1 receptors concentration secondary to chronic low DA levels (Slifstein et al., 2008). This observation, together with reports that clozapine enhance PFC DA release, probably through complex mechanism involving serotoninergic and GABAergic neurons (Cochran et al., 2003, Purkayastha et al., 2012), could suggest that clozapine-induced DA release may exert greater effect in Val/Val subjects, who have higher levels of D1 receptors, key mediators of dopaminergic activity at the PFC. Moreover clozapine, compared to other antipsychotics, displays D1 blockade properties (Tauscher et al., 2004) that could partially compensate the D1 over expression associated to the Val/Val genotype. Finally, chronic treatment with clozapine, but not haloperidol, was reported to be associated with a significant COMT downregulation in rat frontal cortex (Fatemi & Folsom, 2007), possibly leading to a reduced enzymatic activity, as in Met carriers.

It is important to remind that this study presents important limitations. First of all the limited sample size and the greater proportion of patients treated with clozapine, compared to risperidone and mainly to haloperidol. Moreover we did not take into account past treatment history, which is likely to be different between the three groups, with patients in clozapine probably having received more previous treatments. Finally we need to notice that the interaction of pharmacological compound with the underlying biological substrate is likely to be modulated at many different levels by numerous variables including pharmacokinetic and pharmacodynamic factors that were not taken into account.

5. Conclusions

Even if interpretation of results is far from clear, also given the limitations that are discussed above, our study suggests that COMT polymorphism influence negative symptoms response, interacting in opposite direction with antipsychotic with different antidopaminergic profile. Specifically the COMT Val/Val subjects seem to show a greater improvement in negative symptomatology, that is comparable to the improvement observed in Met Carriers treated with haloperidol or risperidone, only when treated with clozapine. In this view the Val/Val genotype could be a promising biological marker for direct treatment with clozapine, at least in patients with prominent negative features.

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