Neuroscience Letters 516 (2012) 85–88

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

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

Influence of *COX-2* and *OXTR* polymorphisms on treatment outcome in treatment resistant depression

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ARTICLE INFO

Article history:
Received 3 February 2012
Received in revised form 20 March 2012
Accepted 22 March 2012

Keywords:
COX-2
OXTR
Major depression
Bipolar disorder
Antidepressants

ABSTRACT

Inflammatory pathways play a crucial role in the pathomechanisms of antidepressant efficacy. The aim of this study was to investigate whether a set of single nucleotide polymorphisms (SNPs) within cyclooxygenase-2 (*COX-2*, rs5275 and rs20417) and oxytocin receptor (*OXTR*, rs53576 and rs2254298) genes was associated with antidepressant treatment resistance, response or remission. Three hundred seventy-two patients were recruited in the context of a multicenter resistant depression study. They were genotyped for *COX-2* and *OXTR* SNPs. Treatment resistance (according to two different definitions), response and remission were recorded. We did not observe any association between the genotypes or alleles of the selected SNPs within *COX-2* and *OXTR* genes and treatment resistance, response and remission in the whole sample. Our results are consistent with those of some studies but not with those of other ones. Indeed, several factors could be involved in the discrepancy observed across studies. They include sample size, environmental factors, differences in ethnicity, different study designs, and different definitions of treatment resistance.

1. Introduction

Major depressive disorder (MDD) is a severe and potentially disabling psychiatric illness that is characterized by a significant change in mood. MDD is a leading cause of disability worldwide [3]. The lifetime incidence in the US is estimated to be 12% in men and 20% in women [11]. Considering that more than 30% of depressed patients is resistant to treatment with available antidepressant medications (mainly based on the 'monoamine hypothesis of depression') [23], there is a pressing need to identify novel pathophysiologic pathways relevant to depression that can aid in identifying and monitoring potentially responsive patients. Many lines of evidence now support the hypothesis that inflammation-related pathways are involved in the pathophysiology of psychiatric disorders, including MDD; moreover, inflammatory mechanisms may also be a target of psychotropic medications, including antidepressants [7,18,19]. Moreover, anti-inflammatory drugs (acetylsalicylic acid) have been reported to accelerate the antidepressant effect in MDD patients [4,17]. An interesting inflammatory signaling pathway is the phospholipase/cyclooxygenase (COX)/prostaglandin (PGE) pathway. Indeed, increased pro-inflammatory cytokines and increased levels of PGE(2) have repeatedly been described in MDD [20]. COX-2 is

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http://dx.doi.org/10.1016/j.neulet.2012.03.063

expressed in neurons of the neocortex and hippocampus under normal physiological conditions, suggesting its essential role in normal neuronal function. Furthermore, COX-2 can be induced in microglia and astrocytes in a variety of pathological conditions including hypoxia and excitotoxins [16]. Interestingly, COX-2 inhibitors, that inhibit the PGE(2) production, were recently found to increase reboxetine effects in MDD patients [20]. Another interesting protein that appears to be involved in inflammatory processes is oxytocin (OXT) [1]. Oxytocin receptors (OXTRs) are G-protein-coupled receptors, their activity is mediated by G proteins which activate a phosphatidylinositol–calcium second messenger system [12]. Oxytocin receptors are also widespread throughout the central nervous system and modulate a variety of behaviors [10]. These include responses to stress and anxiety, social memory and recognition, bonding, and sexual and maternal behaviors [28]. Moreover, recent animal studies suggest that the neuropeptide oxytocin is implicated both in prosocial behavior and in the central nervous control of neuroendocrine responses to stress. Indeed, oxytocin administration and social support increase calmness and reduce anxiety and stress-response [10]. Furthermore, Costa and colleagues showed an involvement of the oxytocinergic system in the mechanisms that underlie depression and specific adult attachment styles [6].

On the basis of such observations and taking into account the dearth of studies focusing on such single nucleotide polymorphisms (SNPs), we aimed to investigate whether a set of SNPs within *COX-2* (rs5275 and rs20417) and *OXTR* (rs53576 and rs2254298) genes was associated with pharmacological treatment resistance, response or remission in an independent sample of MDD and bipolar disorder (BD) patients selected in the context of a multicenter trial on treatment resistance depression.

2. Methods

The sample under investigation in the present paper has been recruited in the context of the European multicenter project 'Patterns of treatment resistance and switching strategies in unipolar affective disorder' and partly reported investigating other candidate genes. Four European centers took part in this project: (i) Department of Psychiatry, Erasme Hospital, Universite Libre de Bruxelles, Brussels, Belgium; (ii) Sint-Truiden, Psychiatric Center, Sint-Truiden, Belgium; (iii) Department of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer, Israel; (iv) Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria. Detailed description of the whole sample was reported elsewhere [26]. Here we report data on a subsample of patients for which genetic data of *COX2* and *OXTR* were available. Briefly, our sample comprised two hundred eighty-six patients with MDD and eighty-six patients with a previous history of BD [25]. Patients have been included if they received at least one adequate antidepressant trial during the current or most recent depressive episode. Two definitions of treatment resistance have been considered in the analyses: (1) non response to at least 2 adequate consecutive antidepressant treatments administered during the last episode [26]; (2) non response to at least 2 adequate consecutive antidepressant treatments of different classes (mechanism of action) administered during the last episode [5]. Non resistant patients reported a Hamilton Depression Rating Scale (HDRS) [9] score $\leq$17 after an adequate antidepressant treatment or at the second trial after a first non response. Non responders were defined as having a HDRS score >17 while non remitters were >7.

The study protocol was approved by the ethical committees of all participating centers. After giving a complete description of the study, written informed consent was obtained from all subjects.

The selection of SNPs under investigation was based on previous research suggesting a possible association between *COX-2* (rs5275 and rs20417) and *OXTR* (rs53576 and rs2254298) genes and antidepressant treatment [10,20].

After extraction of genomic DNA, all SNP regions were separately amplified. Then, ABI Prism SNaPshot Multiplex reactions were performed to purified samples (Table 1). After post-extension treatment, all samples were analyzed using capillary electrophoresis ABI 3130 Genetic Analyzer with GeneMapper ID 4.0 Analysis Software [14].

The main outcome measure of the present study was the influence of the SNPs under investigation on treatment resistance (according to the two described different definitions), response and remission in the whole sample and in the two sub-groups of MDD and BD separately analyzed.

Statistical analyses were performed using 'Statistica' package [27]. The χ^2 statistics was used to test possible influences of specific SNPs in *COX2* and *OXTR* on resistance, response and remission rates to treatment as well as on secondary outcome parameters, such as melancholic features, suicidal risk, lifetime history of suicide attempt, anxiety disorder comorbidity, and age at onset. In case of positive findings, clinical variables correlated with the outcome measures under investigation were added as covariates, so as to investigate possible stratification effects with multivariate methods. The influence of the SNPs under investigation and continuous outcomes was calculated using the ANOVA.

Haploview-3.2 was used to generate a Linkage-Disequilibrium (LD) map and to test for Hardy–Weinberg-Equilibrium (HWE) [2]. Permutations (n = 10,000) were performed. Despite the exploratory nature of our study, all p-values were 2-tailed, and statistical significance was conservatively set at the 0.001 level (corresponding to the Bonferroni correction for the 10 variables under investigation) in order to reduce the likelihood of false positive results. With these parameters we had a sufficient power (0.80) to detect a small-medium effect size (ω = 0.25) for case–control analyses that, as an example, corresponded to an odds ratio of 2.84 between the two groups of patients and the group of controls.

Table 1
Considered SNPs and used primer sequences in this study.[a]

dbSNP	Position[b]/location	Seq. change	PCR primers	SNP primers
COX2				
rs5275	chr1:1866430586502 3′ UTR	C>T	5′-TTCCAATGCATCTTCCATGA-3′ 5′-TCAAACAAGCTTTTACAGGTGA-3′	5′-GATCGATCGATCAAATTTTAAAGTACTTTTGGT-3′
rs20417	chr1:186650321(−762) Promoter	C>G	5′-CATTTAGCGTCCCTGCAAAT-3′ 5′-TACCTTCACCCCCTCCTTGT-3′	5′-TCCTTGTTCTTGGAAGAGAGG-3′
OXTR				
rs53576	chr3:8804371(6930) Intron	A>G	5′-GCCCACCATGCTCTCCACATC-3′ 5′-GCTGGACTCAGGAGGAATAGGGAC-3′	5′-GATCGAAAGGTGTACGGGACATGCCCGAGG-3′
rs2254298	chr3:8802228(9073) Intron	A>G	5′-TGAAAGCAGAGGTTGTGTGGACAGG-3′ 5′-AACGCCCACCCCAGTTTCTTC-3′	5′-GATCGATCGATCAAGAAGCCCCGCAAACTG-3′

[a] www.snpper.chip.org.
[b] Absolute chromosomal position. The relative position to the start codon is given in parenthesis.

Table 2
Clinical and demographic characteristics of the sample.

Clinical and demographic characteristics	Cases (n = 372)
Diagnosis	
Unipolar depression	286 (77%)
Bipolar disorder	86 (23%)
Gender	
Males	103 (29%)
Females	260 (71%)
Age	50.8 ± 14.16
Ethnicity (Caucasians)	352 (99%)
Marital status	
Married or living with someone	208 (56%)
Smokers	137 (38%)
Age first Episode	37.74 ± 16.08
Melancholic features	242 (66%)
Suicidal risk	220 (60%)
Comorbidity with an anxiety disorder	123 (34%)
Suicidal attempt	117 (33%)
Responders	160 (43%)[a]
Remitters	67 (18%)[b]
Resistance (1)	154 (57%)[c]
Resistance (2)	86 (25%)[d]

[a] The percentage is referred to available data (371 patients).
[b] The percentage is referred to available data (363 patients).
[c] The percentage is referred to available data (268 patients).
[d] The percentage is referred to available data (345 patients).

3. Results

Socio-demographic and clinical features of our sample are reported in Table 2. Pertaining to treatment resistance, data were available only for 268 patients (72% of the entire sample). However, this sub-sample of subjects without treatment resistance data did not differ from the overall sample in terms of socio-demographic or clinical variables and in terms of allelic and genotype frequencies.

COX-2 and *OXTR* were in HWE in the whole sample: (*COX-2* rs5275 Hwpval = 0.8676; *COX-2* rs20417 Hwpval = 1.0; *OXTR* rs53576 Hwpval = 0.119 and *OXTR* rs2254298 Hwpval = 0.0632). We did not observe any association between genotypes or alleles under investigation and treatment resistance (according to both definitions), response and remission in the whole sample and in the two diagnostic sub-groups (MDD and BD) separately analyzed (all p values > 0.001; Supplemetary table). We found no association with treatment resistance considering both definitions. Multivariate analyses did not yield different results.

Regarding secondary analyses, no association was found between genotypes or alleles and melancholic features, suicidal risk, lifetime history of suicide attempt, anxiety disorder comorbidity (all p values > 0.001; Supplementary table) and age at onset (data not shown).

We observed an association between *OXTR* rs2254298 AA genotype and MDD subgroup in comparison with BD subgroup (http://snpper.chip.org) (χ^2 = 13.933, p-value = 0.00094, Table 3). Furthermore, a similar association was observed in the allelic analysis as well (χ^2 = 15.06, p-value = 0.0001, Table 3). Interestingly, BD patients had frequencies similar to the general population as reported in international databases with respect to Caucasian samples.

4. Discussion

In the present study we found no association between *COX-2* (rs5275 and rs20417) and *OXTR* (rs53576 and rs2254298) variants and treatment resistance (according to two definitions), response or remission in a sample of MDD and BD patients.

However, an association between *OXTR* rs2254298 and MDD subgroup both in genotypic and allelic analyses has been observed. This is in agreement with a recent report highlighting the potential importance of this same polymorphism in the etiology of both depressive and anxiety symptoms [28]: in particular, rs2254298

Table 3
Differences between genotype and allelic frequencies between subjects with major depression and bipolar disorder. General population frequencies from international databases with respect to Caucasian sample are also reported for reference (http://snpper.chip.org).

Bipolar disorder	Major depression	General population	χ^2	p-Value
Allele frequency				
COX2 rs5275				
C: 52 (30%)	C: 185 (33%)	C: 37%	0.553	0.457
T: 120 (70%)	T: 371 (67%)	T: 63%		
COX2 rs20417				
C: 25 (15%)	C: 105 (20%)	C: 18%	2.3955	0.121
G: 147 (85%)	G: 425 (80%)	G: 82%		
OXTR rs53576				
A: 60 (35%)	A: 166 (30%)	A: 39%	1.647	0.199
G: 110 (65%)	G: 386 (70%)	G: 61%		
OXTR rs2254298				
A: 7 (4%)	A: 87 (15%)	A: 7%	15.06	0.0001
G: 165 (96%)	G: 481 (85%)	G: 93%		
Genotype frequency				
COX2 rs5275				
CC: 8 (9%)	CC: 29 (11%)	CC: 13%	0.565	0.753
CT: 36 (42%)	CT: 126 (45%)	CT: 50%		
TT: 42 (49%)	TT: 123 (44%)	TT: 37%		
COX2 rs20417				
CC: 1 (1%)	CC: 10 (4%)	CC: 70%	2.365	0.306
CG: 23 (27%)	CG: 83 (31%)	CG: 24%		
GG: 62 (72%)	GG: 172 (65%)	GG: 6%		
OXTR rs53576				
AA: 6 (7%)	AA: 26 (9%)	AA: 8%	5.75	0.056
AG: 48 (57%)	AG: 115 (42%)	AG: 52%		
GG: 31 (36%)	GG: 135 (49%)	GG: 40%		
OXTR rs2254298				
AA: 0 (0%)	AA: 9 (3%)	AA: 0%	13.933	0.00094
AG: 7 (8%)	AG: 68 (24%)	AG: 15%		
GG: 79 (92%)	GG: 207 (73%)	GG: 85%		

seemed to interact with an adverse parental environment (mothers' history of recurrent MDD) to predict these symptoms in adolescent girls.

The potential role of COX-2 and OXT in mood disorders has been further hypothesized. While the use of COX-2 inhibitors in association with reboxetine was found to increase symptomatological improvement in MDD patients [20], contrasting results have been reported regarding the potential role of OXT in depression [6,8,22,24,29]. This nonapeptide hormone has however been found to attenuate the stress response in both rats and humans [15]. Moreover, intracerebral oxytocin has been shown to inhibit the responsiveness of the hypothalamic–pituitary–adrenal axis in rats [21], and intranasal administration of oxytocin has been associated with decreased amygdala activation in response to threatening scenes in humans [13].

Possible explanations for the discrepancy observed between the results of the present study and those of other studies could be imputed to the use of different treatments, the investigation, in some cases, of different SNPs, the different ethnicity of patients, the sample size and the environmental factors. Moreover, the limited sample size of our study could raise concerns as to whether negative observed findings could simply reflect the lack of statistical power to detect small differences such as those that are likely to be associated with single SNPs. Furthermore, it should be acknowledged that the power of the subanalyses might have been even more compromised by small numbers. In addition, the retrospective assessment of data about duration and adequacy of antidepressant treatments should also be taken into account. In conclusion, our preliminary data suggest that the SNPs under investigation are not associated with the treatment outcome in our sample of MDD and BD patients. However, taking into account the limitations stated above and considering the possible involvement of the biological pathway under investigation in our study, independent replications with larger sample sizes are needed in order to better understand the potential role of *COX2* and *OXTR* on the short and long term antidepressant treatment outcome.

Acknowledgments

The study was sponsored by Lundbeck A/S and the Belgian National Fund for Scientific Research (FNRS; 3.4.530.07 F) by means of an unrestricted grant for the Group for the Study of Resistant Depression (GSRD). The sponsors had no role in the study design, analysis and writing of the paper. All authors were actively involved in the analytical method of the study, selection and review of all scientific content and had full editorial control during writing of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2012.03.063.

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