

Beta Adrenoceptor Polymorphism and Clinical Response to Sertraline in Major Depressive Patients

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Received, October 31, 2016; Revised, December 2, 2016; Accepted, January 11, 2017; Published, January 11, 2017.

ABSTRACT – Purpose: The adrenoceptor family, as one of the main contributors in regulating the noradrenergic system, has been studied in involvement of depression and its treatment. A functional polymorphism of G1165C on beta adrenoceptor (β AR) enhances post receptor signalling and is assumed to be involved in pharmacotherapy of depression. The aim of the present study was to discern the influence of G1165C polymorphism in the β 1AR gene on individual differences in response to sertraline. **Methods:** One hundred newly diagnosed patients completed 6 weeks of sertraline treatment. Response to treatment was defined as a 50% decrease in Hamilton Rating Scale for depression (HRSD). **Results:** The patients who carried CC genotype responded five times more to sertraline comparing with other variants ($P=0.005$; $OR=5.7$; $95\%CI=1.4-23.9$). Moreover, carriers of C allele responded three times more to sertraline than patients with the G allele ($P=0.001$; $OR= 3.3$; $95\%CI= 1.72-6.50$). **Conclusion:** In conclusion, our results support the hypothesis that genetic variation of β 1AR might influence clinical response to sertraline.

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INTRODUCTION

Major depressive disorder (MDD) being a common illness is assumed to be moderately inherited (1). The heritability of MDD is estimated to be about 31–42% (2, 3). A significant association between excess mortality and depression has been reported in various samples (4, 5). It has long been theorized that monoamines as neurotransmitters are involved in the pathogenesis of mental disorders such as depression (6, 7). Monoamine theory implies that depression is due to changes of brain monoaminergic activity and that antidepressants alter this activity (8, 9). Considerable clinical evidence support the crucial role of norepinephrine (NE) and serotonin in etiology of MDD (10-12). It is crystal clear that antidepressants eventually increase the synaptic concentration of these monoamines resulting in long-term adaptive changes (7). The central noradrenergic system, anatomically based in the locus coeruleus (LC) of brain stem, is responsible for noradrenergic neurotransmission in the brain and plays a pivotal role in cognitive processes

(13). The actions of NE are mediated by the family of G protein-coupled receptors (GPCRs) known as the adrenoceptors (ARs) (14).

Antidepressants can target almost all components of the monoaminergic system to induce their pharmacological actions (15, 16). Most genetic studies have considered set of functional polymorphisms relevant to monoaminergic neurotransmission in depression (17-19). The ARs, consisting of β , α_1 , and α_2 receptors, are the cellular mediators of noradrenergic neurotransmission. The β ARs are classified in three groups of β_1 , β_2 and β_3 . The most frequent subtype in mammalian brain is β_1 which controls physiological responses to catecholamines. β_1 AR was mapped on chromosome 10q24-q26. Studies have manifested a relationship between this region and depressive disorders (20, 21). All β

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receptor subtypes couple to the stimulatory G-protein (Gs) therefore activate the cyclic adenosine monophosphate (cAMP) signalling. Regarding the association between upregulation of β ARs and depression it may be concluded that some classes of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) may downregulate and desensitize these receptors in brain (22, 23). The functional polymorphism, G1165C, causing an amino acid variation Gly389Arg in the β AR gene was recently identified. Several lines of study suggest that C allele of this polymorphism may enhance coupling to the Gs protein and thereafter increase adenylyl cyclase activation (24, 25).

The pharmacological treatment of depression has been the centre of attention for many years. Although pharmacotherapy has alleviated morbidity of individuals with depression, only 30-40% of patients seem to respond completely to treatment (26). Among the antidepressants, the SSRIs are common first line treatments, especially due to their minimal adverse effects and good tolerability (27). It is believed that they are effective in brain adrenergic function as well which corroborate their non-serotonin dependant mechanism as a therapeutic option for MDD (28, 29).

To the best of our knowledge, the association between β ARs polymorphisms and response to sertraline has not yet been studied. Inter-individual variations in response to different SSRIs lead us to the hypothesis that therapeutic outcome might be partly influenced by genetics of β ARs. Therefore we investigated, for the first time, the association between G1165C polymorphism and sertraline treatment outcome in a population of depressed patients.

METHODS

Study population

This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and Uniform Requirements for manuscripts submitted to biomedical journals. This work study was approved by the local committee for ethics of medical experiments on human subjects of Shiraz University of Medical Sciences. We obtained written consent from all participants prior to the interview. All patients were unrelated, of Caucasian origin and from the same geographical area.

Patients were recruited between 2011 and 2012 in Hafez hospital, Shiraz University of Medical

Sciences and followed during 6 weeks by an experienced psychiatrist. A total of 100 newly diagnosed MDD patients (male: 25, female: 75, mean age \pm S.D.: 35.5 \pm 12.9) according to DSM V criteria were included in the study. Newly diagnosed was defined as a negative previous diagnosis of depression and no history of antidepressant medications use. An initial 21-item Hamilton Depression Rating Scale (HDRS) was used to evaluate the severity of depression (30). Exclusion criteria were as follows: anxiety disorders, a family history of schizophrenia, a personal history of bipolar disorder, a family history of bipolar disorder in first-degree relatives; a personal history of schizophrenia, manic or hypomanic episode, mood incongruent psychotic symptoms, active substance dependence, and current treatment with antipsychotics or mood stabilizers.

Drug administration

Sertraline (SERTRALINE-ABIDI[®]) was administered at a fixed-dose regimen of 50 mg for one week initially. The dose could be increased by 50mg/day per week to a maximum of 200 mg/day according to clinical response over the 6 week treatment duration. Only hypnotics such as zolpidem or anxiolytics such as chlordiazepoxide were allowed for severe anxiety. A positive clinical response to sertraline treatment was considered if at least 50% reduction in the baseline HDRS score was observed through the sixth week. Evaluations were done at baseline, weeks 1 and 6 of treatment. Prior to interviewing, 5ml of venous blood samples were collected for further genotyping

DNA extraction and genotype determination

DNAs were extracted from leukocytes of whole blood using a salting out method (31). PCR amplification of G1165C was performed using primers mentioned in Table 1. Genotyping of G1165C was done as described previously by Moriyama et al. (32). An Eppendorf gradient Master cycler (Hamburg, Germany) PCR machine was used as the thermal cycler. PCR products (7 μ l) were digested with Mva I (TaKaRaBio). Electrophoresis on 3 % agarose (Invitrogen[®] Ultra Pure) gel was used to separate digested fragments. They were then stained by ethidium bromide and visualized in a UV trans illuminator. It is to mention that all of the samples were genotyped at least twice and reconfirmed.

STATISTICS

SPSS® 21.0 for windows® was used for data analysis (SPSS Inc., Chicago, Illinois). Hardy–Weinberg equilibrium (HWE) for distribution of genotypes was calculated by chi-square (χ^2) test. Continuous variables are revealed as mean \pm S.D. Genotype frequencies are presented in percentage (%). Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. Associations between categorical variables were calculated by Pearson's chi-square or Fisher's exact test and for interval data by Student's t-test. χ^2 test was performed for univariate analysis of genotypes. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. P value <0.05 was considered as statistically significant.

RESULTS

In terms of response, 33 patients (33%), were responders to sertraline (baseline HDRS: 26.1 \pm 10.2; HDRS after week 6: 11.1 \pm 7.5) and 67 patients (67%), were non-responders (baseline HDRS: 26.3 \pm 9.5; HDRS after week 6: 21.9 \pm 9.5). Demographic data of patients are demonstrated in Table 2. Table 3 shows genotype and allele frequencies of patients receiving sertraline based on

50% score reduction. Patients carrying CC genotype responded significantly more to sertraline than patients carrying either GG or GC genotypes (P=0.005; OR=5.7; 95%CI=1.4-23.9). Moreover, carriers of C allele responded by 3.3 fold better to sertraline than carriers of G allele (P=0.001; OR=3.3; 95%CI= 1.72-6.50).

DISCUSSION

As to our knowledge, this is the first study examining the association of G1165C polymorphism on β_1 ARs gene and response to sertraline in a population of newly diagnosed Iranian MDD patients. The inspiration of the present study was the significant role of β ARs in neural and autonomic functions (33, 34) and the important contribution of genetics on the outcome of antidepressant pharmacotherapies (26, 35).

The novel findings of our study is the significant association of CC genotype of G1165C with response to sertraline. Patients carrying the CC genotype responded 5.7 fold more to sertraline comparing to carriers of other variants (P=0.005, OR=5.7; 95%CI=1.4-23.9). Also carriers of the C allele represented 3.3 fold better response to sertraline comparing with other variants (P=0.001, OR=3.3; 95%CI=1.72-6.50).

Table 1. Primers, PCR condition and locations of β_1 AR, G1165C polymorphism on DNA.

Polymorphisms	Primer sequence (5'-3')	Location	Restriction enzyme	Allele	DNA fragment size (bp)	References
G1165C (<i>β_1AR</i>)	F- ACGCTGGGCATCA TCATGGGC R- ACATCGTCGTCGT CGTCGTCC	chromosome (10q25.3)	<i>MvaI</i> at 37 °C/16 hrs	G C	280/52 142/138/52	(Zill et al., 2003)

PCR: Polymerase Chain Reaction; *β_1 AR*: Adrenergic beta receptor 1, F: Forward primer, R: Reverse primer.

Table 2. Demographic characteristics of patients responsive to sertraline.

Variables	Responders (n=33)	Non-responders (n=67)	P-value
Sex (male/female)	9/24	16/51	0.713
Age (years)	35.2 \pm 13.7	35.4 \pm 12.5	0.936
HAMD score 1 (before treatment)	26.1 \pm 10.2	26.3 \pm 9.5	0.911
HAMD score 2 (after treatment)	11.1 \pm 7.5	21.9 \pm 9.5	0.0001

Table 3. Genotype and allele frequencies of G1165C variant in patients receiving sertraline.

Polymorphism	Genotype	Responders (n=33)	Non-responders (n=67)	P_C	OR; 95% CI
Genotypes				0.003	5.7; 1.4-23.9
	GG	13 (39.4%)	46 (68.6%)		
	GC	12 (36.4%)	18 (26.9%)		
	CC	8 (24.2%)	3 (4.5%)		
Alleles				0.0002	3.3;1.72-6.50
	G	38 (57.6%)	111 (82.8%)		
	C	28 (42.4%)	23 (17.2%)		

P_C : P-value for χ^2 test, OR: Odds Ratio, CI: Confidence interval

While world-wide rate of depression is rapidly increasing(36), response to antidepressants and remission is fairly satisfactory (37). Although many studies bold the contribution of genetics in predisposition to MDD, its role as therapeutic determinant remains obscure.

β_1 ARs belong to the family of GPCRs representing the leading target for modern drug therapy (38). GPCRs is a foremost contributor to the pathophysiology of several mental illnesses(39, 40). Several lines of evidence have proven the consistent and significant role of adrenergic system in affective disorders. Between components of beta adrenergic system, β_1 ARs have been broadly studied and seem to have major contribution in the pathophysiology of depression(41, 42). Chronic treatment with most antidepressant drugs leads to down regulation and desensitization of β_1 ARs in particular regions of brain especially the hippocampus, and not the β_2 ARs. Pharmacological effect of antidepressants showing 10 -30 more affinity for β_1 receptors than β_2 is a good justification for this finding (43-45).

Biochemical, anatomical and electrophysiological data indicate a reciprocal interaction between the serotonergic and adrenergic systems (46). This may explain why intact serotonergic system is essential for pharmacologic actions of tricyclic antidepressants as well (47). On the other hand administration of sertraline resulted in reduction in number of beta adrenoceptors in rat (46) which suggests an effective interaction of sertraline with these receptors. The interplay of adrenoceptor and serotonergic systems in the brain, aside from the effects of SSRIs on the reuptake of norepinephrine, is further described by the role of catecholamines in

the pathophysiology of depression (48) where the effects of major anti-depressant medications can be echoed in those with augmented adrenergic responses. Together with the abundance of norepinephrine (secondary to its reuptake inhibition) and the downregulation of adrenoceptors by sertraline, certain polymorphisms of adrenoceptor gene, G1165C in this study, is shown to be effective in therapeutic response in sertraline users.

The β_1 AR gene is located in 10-24q-26 region (49) and the functional common polymorphism happens in G1165C nucleotide that induces an amino acid substitution from glycine to arginine at position 389 β_1 AR, the region that located in fourth intracellular loop of receptor and is very important for the coupling to G_s . In other words presence of C allele enhances the coupling of G_s and consequently increases the level of cAMP and signal transduction. Signal transduction cascade has very important role in implement of drug effect. The C allele by inducing signal transduction and second messenger activity leads to vast transcription factors level. As a consequence elevated transcription factors regulate gene expression that cause down or up regulation of the number and sensitivity of receptors or amount of inhibitory or stimulatory G proteins by feedback mechanisms and therefore is responsible for more adaptive drug responses (24). All together may explain our finding that carriers of the C allele responded better to treatment than carriers of the G allele.

A study conducted by Crowley et al., showed lack of association between the investigated functional polymorphism (G1165C) and response to citalopram in depressed patients although the region containing this variant strongly influenced response

to citalopram in a mouse model of depression. It is to note that in the mentioned study, ethnic differences was detected in genotype and allele frequencies (50). On the other hand, as reported previously by Zill et al this variant is not associated with either MDD nor antidepressant response but the C allele might be an indicator for a more rapid and maybe even better response to antidepressant medication (25). It is worthy of mentioning that different categories of antidepressants were used in the study conducted by Zill et al, and not a certain drug, but our study was restricted to examining the effect of genetic variations on response to an SSRI like sertraline. Thus, these studies may boost the assumption about the role of G1165C polymorphism in antidepressant outcome.

Recruiting solely the newly diagnosed MDD patients with two conditions: the absence of concomitant psychiatric disorders and parallel medication use; may approximate a cause and effect relationship in our results. Keeping the major confounders at a minimum level, our observational study could well demonstrate the relation of a better response rate to sertraline with carrying the C allele of β_1 AR gene. To provide stronger evidence to support our findings, we recommend the conduct of a randomized controlled trial of sertraline versus placebo in G and C allele carriers. Besides regarding conflicting reports suggesting diverse responses to therapy in C allele carriers in different populations, replication studies are warranted.

It would be worth mentioning that involvement of genetics in pharmacotherapy is a part of several mechanisms leading to different treatment outcome. Depression and other multifactorial affective disorders are more complex than could be interpreted by only one mechanism and β_1 AR variants may have a minor role in response to treatment.

CONCLUSION

Our result suggests that functional genetic variant in β ARs would be a predictor for response to sertraline. However; further investigations about different variants of ARs may provide more promising data for individualized therapy in depression.

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