An association of AKT1 gene polymorphism with antidepressant treatment response

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ABSTRACT

Objectives: Nowadays it is considered that protein kinase Akt1 could be involved in pathogenesis of affective disorders. We have examined whether AKT1 gene polymorphisms are associated with antidepressant treatment response.

Methods: The study included 106 Caucasian patients with depressive disorders from Siberia and 103 healthy control donors. The frequencies of single nucleotide polymorphisms rs1130214 and rs3730358 of AKT1 gene were examined.

Results: A comparison of genotypic or allelic frequencies between the groups of healthy donors and depressive patients showed no statistically significant difference. No association between the polymorphisms under study and the scores according to Hamilton Depression Rating Scale 17 was found. However, an association between treatment response assessed by the Clinical Global Impression – Improvement scale and rs1130214 polymorphism was observed.

Conclusions: AKT1 gene polymorphism rs1130214 is associated with antidepressant treatment response in patients with depressive disorders.

Introduction

Nowadays depression is considered to be a heterogeneous, highly widespread and severe recurrent mental disorder linked to diminished role functioning and quality of life, medical morbidity and mortality (Üstün et al. 2004). The World Health Organisation ranks depression as the fourth leading cause of disability worldwide, and projects that by 2020 it will be the second leading cause (Murray and Lopez al. 1996a,b).

Recent studies have shown that dysregulation of intracellular signalling pathways plays an important role in mental disorders pathogenesis. Nowadays protein kinases involved in neurobiological processes are believed to be new targets for pharmacotherapy, prognosis and diagnostics of affective disorders (Dunman 2013).

Protein kinase Akt1 (PKBx) (an isoform of protein kinase B) is intracellular signalling serine/threonine kinase which is ubiquitously expressed through the body. Akt1 is activated through phosphorylation by two main residues: threonine 308 by 3-phosphoinositide-dependent kinase-1 (PDK1) and serine 473 by mTOR complex 2 (Gonzalez and McGraw 2009). Regulation of Akt/mTOR pathway is a critical signalling pathway in synaptic neurotransmission and plasticity, also modulating cell proliferation and migration (Machado-Vieira et al. 2015). Akt1 plays an important role in cell development, growth and survival in the nervous system. Its expression in the nervous system is substantially up-regulated during cellular stress, suggesting a more expansive role for Akt1 in the nervous system that may involve cellular protection (Chong et al. 2005). Also Akt1 is involved in signalling pathways of various growth factors (brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF)) and neurotransmitters such as serotonin and dopamine (Beaulieu 2012).

Nowadays a large number of studies are dedicated to the role of Akt proteins in mental disorders. Emamian et al. (2004) found a significantly lower level of Akt1 protein in the peripheral lymphocytes of schizophrenics and in post-mortem samples of the frontal cortex and hippocampus. Post-mortem studies of cortical regions obtained from depressed subjects have also shown reductions in Akt function (Hsiung et al. 2003; Karege et al. 2007). Attenuation of the kinase activity of Akt1,
combined with the dysregulation of PTEN and PI3K in depressed suicide victims, may result in insufficient phosphorylation of lipid second messengers (Karege et al. 2011). Machado-Vieira et al. (2015) showed decreased Akt1 and mTOR expression in blood of bipolar patients; also changes in Akt1 expression after lithium treatment were positively correlated with depression improvement. Previously we showed low levels of total Akt1 and its phospho-serine 473 form in peripheral blood mononuclear cells of patients with depressive disorders which could be a sign of neurodegenerative process in the brain (Losenkov et al. 2014). Recent reviews examined the role of Akt and glycogen synthase kinase-3 as well as Akt/mTOR signalling pathway in various psychiatric illnesses, focussing on their interactions with dopaminergic and serotonergic pathways, as well as the effects of antipsychotics, antidepressants and lithium (Beaulieu et al. 2009; Cohen 2013; Abelaira et al. 2014).

SNPs rs1130214 and rs3730358 were selected because previous work showed their association with bipolar disorder and major depression (Magno et al. 2010; Pereira et al. 2013). We chose these SNPs because a previous study demonstrated their association with higher Akt1 level (Emamian et al. 2004). Also there are no data about association of these SNPs with antidepressive therapy response.

Therefore, it makes AKT1 gene a possible candidate for investigation of depressive disorders pathogenesis as well as their clinical polymorphism and therapy response.

We investigated whether AKT1 gene polymorphisms rs1130214 and rs3730358 are associated with depressive disorders, severity of depressive symptoms assessed by Hamilton Depression Rating Scale 17 and antidepressant treatment response evaluated by the Clinical Global Impression – Improvement Scale in Caucasian psychiatric patients from Siberia (Russia).

Materials and methods

Subjects

After the approval of the study protocol by the Institutional Medical Review Board, participants were recruited from psychiatric departments of the Mental Health Research Institute in Tomsk, Siberia (Russia). All subjects gave written informed consent after a proper explanation of the prospective study.

We included patients with depressive disorders diagnosed by the following: depressive episode (ICD-10: F32) and recurrent depressive disorder (ICD-10: F33). The control group also included mentally and physically healthy donors. Subjects with non-Caucasian physical appearance were excluded from the study.

Clinical and demographic data were extracted from the patients’ medical files. For assessment of depression severity Hamilton Depression Rating scale 17 (HDRS-17) was used (Hamilton 1960). Assessment was made at baseline and after 14 and 28 days of treatment. For the evaluation of the antidepressant treatment response we used the Clinical Global Impression - Improvement Scale (CGI-I) (Guy 1976). Evaluation was made after 14 and 28 days of treatment.

Medication

Patients were given the following groups of antidepressants: selective serotonin reuptake inhibitors (escitalopram, fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram) (57.9%), tricyclicantidepressants (clomipramine, pipofezine) (20.0%), serotonin–norepinephrine reuptake inhibitors (duloxetine, venlafaxine) (7.1%), noradrenergic and specific serotonergic antidepressants (mirtazapine, mianserin) (2.7%) and agomelatine (12.3%). All antidepressants were used in recommended average therapeutic doses. The course of treatment was 28 days long.

Genotyping

DNA extraction was performed by the absorbent method using a “Silica” kit (Medigen) and blind to the clinical status of the subjects. Single nucleotide polymorphisms (SNP) rs1130214 and rs3730358 were genotyped by polymerase chain reaction using the fluorogenic 5’-exonuclease TaqMan technology and an amplifier real-time polymerase chain reaction system “StepOne Plus” (Applied Biosystems).

Statistics

The Hardy–Weinberg equilibrium of genotypic frequencies was evaluated using the chi-square test. Statistical analyses were performed using the SPSS software, release 20.0, for Windows. P values less than 0.05 were considered as significant. The chi-squared test was used for between-group comparison of genotypic or allelic frequencies. Between-group differences in continuous variables were evaluated using the Student’s t-test or one-way analysis of variance.

Results

Demographic features

A total of 103 healthy donors and 106 patients with depression were included in the analysis. The group of patients included 60 individuals with depressive episode (ICD-10: F32) and 46 with recurrent depressive disorder.
Table I. Demographic features of studied populations (Student’s t-test).

| Group                        | Gender | Age (M ± σ) |
|------------------------------|--------|-------------|
|                              | Male   | Female      |
| Healthy donors (n = 103)     | 14.3   | 15          |
|                              | 15     | 85.7        |
|                              | 88     | 37.1        |
| Depressive disorders (n = 106)| 15.7   | 17          |
|                              | 17     | 84.3        |
|                              | 89     | 49.6        |
|                              | 49.6   | 10.8*       |
| Depressive episode (n = 60)  | 19.6   | 12          |
|                              | 12     | 80.4        |
|                              | 48     | 47.4        |
|                              | 47.4   | 11.4        |
| Recurrent depressive disorder (n = 46)| 10.9 | 5          |
|                              | 5      | 89.1        |
|                              | 41     | 52.3        |
|                              | 52.3   | 9.5         |
| Total                        | 22.8   | 42          |
|                              | 42     | 77.2        |
|                              | 77.2   | 183         |
|                              | 183    | 46.6        |
|                              | 46.6   | ± 12.4      |

rs3730358 A/A 2.2 2.9

rs1130214

Healthy donors (n = 103) 14.3 15 85.7 88 37.1 ± 10.9
Depressive disorders (n = 106) 15.7 17 84.3 89 49.6 ± 10.8*
Depressive episode (n = 60) 19.6 12 80.4 48 47.4 ± 11.4
Recurrent depressive disorder (n = 46) 10.9 5 89.1 41 52.3 ± 9.5
Total 22.8 42 77.2 183 46.6 ± 12.4

*P < 0.01 comparing to healthy donors group.

Table II. Genotype and allele frequencies (%) of the polymorphisms of rs1130214 and rs3730358 AKT1 gene in groups of patients and healthy donors (chi-squared test).

| Polymorphism | Genotype | Healthy donors (n = 103) | Patients with a depression (n = 106) | χ², P values |
|--------------|----------|--------------------------|-------------------------------------|-------------|
| rs1130214    | A/A      | 9.2                      | 9.0                                 |             |
|              | A/C      | 45.0                     | 38.6                                |             |
|              | C/C      | 45.8                     | 52.4                                |             |
|              | A        | 37.1                     | 28.3                                | χ² = 1.222, P = 0.804 |
|              | C        | 62.9                     | 71.7                                |             |
| rs3730358    | A/A      | 2.2                      | 2.9                                 |             |
|              | A/G      | 28.3                     | 27.6                                | χ² = 0.058, P = 0.841 |
|              | G/G      | 69.5                     | 69.5                                |             |
|              | A        | 16.3                     | 16.7                                | χ² = 0.331, P = 0.564 |
|              | G        | 83.7                     | 83.3                                |             |

(Table I presents the major demographic features of the studied populations.

**Genotype and association analysis**

Genotype and allele distribution is detailed in Table II. The genotype distribution of AKT1 gene polymorphisms rs1130214 and rs3730358 was consistent with the Hardy–Weinberg equilibrium (P > 0.05). No differences in genotype and allele distribution were found between men and women (see Supplementary Table 1 available online). A comparison by means of the chi-squared test between the genotype and allele frequencies of rs1130214 and rs3730358 SNP in the groups of healthy donors and patients with depressive disorders showed no significant differences (P > 0.05) (see Table II).

**Correlation between severity of depression symptoms, antidepressant treatment response and AKT1 gene polymorphisms**

A comparison of the HDRS-17 score at baseline and after 14 and 28 days of treatment between different genotypes of rs1130214 and rs3730358 SNP of AKT1 gene was made. No difference between the HDRS-17 scores in the patients with different genotypes of rs1130214 and rs3730358 SNP was found (see Supplementary Table 2 available online). We compared CGI-I scores after 14 and 28 days of treatment between different genotypes. The data are presented in Table III. As seen from Table III, the individuals with genotype CC had a higher CGI-I score (P = 0.017) after 28 days of treatment compared with patients with the other genotypes.

**Discussion**

We have described the results of a possible association between rs1130214 and rs3730358 SNP of AKT1 gene and severity of depressive symptoms and antidepressant treatment response in Slavonic Caucasian patients with depressive disorders from Siberia. We found no association between the SNPs under study and depressive disorder. Also no evidence of their association with the severity of depressive symptoms was observed. We found that individuals with genotype CC of SNP rs1130214 have a higher CGI-I score after 28 days of antidepressant treatment which could be considered as a sign of a lower response to therapy.

AKT1 gene is localised on the 14q32.32 chromosome (Gonzalez and McGraw 2009). SNP rs1130214 is located in intron 1 of the gene. SNP rs3730358 is localised in intron 3 of AKT1 gene. Our data concerning no association between SNP rs3730358 and depressive disorder does not correspond to those of a previous study (Pereira et al. 2013). This could be because, in that work, research was made on a Brazilian sample population. No data about association between SNP rs1130214 and depressive disorders have been previously reported. Also, for the first time we have demonstrated that SNP rs1130214 and rs3730358 are not associated with the severity of depressive symptoms. Of special interest is that the patients with AA and A/C genotype of rs1130214 had better response to therapy. This could be explained by the fact that allele A is associated with higher expression of Akt1 (Emamian et al. 2004) and as a consequence has a protective effect.

Possible limitations of this study are the small sample size, cross-sectional design and the heterogeneity of the...
antidepressive medication. Our results suggest that SNP rs1130214 is relevant for antidepressant treatment response in patients with depressive disorders and may be a potential biomarker of the efficacy of psychopharmacotherapy.

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Statement of interest

None to declare.

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