Relation between functional polymorphism of catalase gene (-262C>T) and recurrent depressive disorder

Piotr Galecki [1], Janusz Szemraj [2], Krzysztof Zboralski [1], Antoni Florkowski [1], Andrzej Lewinski [3]

1. Department of Adult Psychiatry, Medical University of Lodz, Poland
2. Department of Medical Biochemistry, Medical University of Lodz, Poland
3. Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland

Correspondence to: Prof. Andrzej Lewiński M.D., Ph.D.
Department of Endocrinology and Metabolic Diseases, Medical University of Łódź, Polish Mother`s Memorial Hospital – Research Institute, Łódź
281/289, Rzgowska St., 93-338 Łódź, Poland.
alewin@csk.umed.lodz.pl

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Abstract

Numerous studies have provided information indicating the involvement of oxidative stress in the pathophysiology of depressive disorder (DD). The antioxidative system protects against the effects caused by reactive oxygen species (ROS). Catalase (CAT) is one of antioxidative enzymes observed to change their levels in the course of depression. The enzyme decomposes hydrogen peroxide (H_2O_2), whose overproduction is a result of many processes taking place in depression. Therefore, functional polymorphism of the CAT gene can be a candidate marker of the risk of depression.

The presented study assessed the correlation between -262C>T polymorphism of the CAT gene, which influences the increase of CAT expression and activity, and the risk of depression development. The study, carried out on a homogeneous group recruited from the Polish population, enrolled 149 healthy subjects and 149 depressive patients. The groups were age-matched.

The obtained results indicate no correlation between -262C>T polymorphism of the CAT gene (both with respect to genotype distribution and allele frequency) and the risk of depression. Nevertheless, further studies assessing the correlations between depression and polymorphism of the genes encoding antioxidative enzymes on larger groups of subjects should be undertaken.

BACKGROUND

Studies aimed at determination of both non-genetic and genetic etiology of neuropsychiatric diseases, including depressive disorder (DD) have been conducted for many years (Leonard, 2001; Levinson, 2006).

There are reports indicating the occurrence of oxidative processes resultant from overproduction of reactive oxygen species (ROS) in DD (Khanzode *et al.* 2003; Lucca *et al.* 2009a; Lucca *et al.* 2009b). The main representatives of ROS and their derivatives include, among others: superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$). ROS are highly active molecules, whose overproduction results in multiple damages to lipids, proteins and nucleic acids, disturb-

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ing normal cellular function, which may also lead to cell death (Valko *et al.* 2007). Brain cells in depression are particularly exposed to oxidative stress and over production of H_2O_2 considering increased activity of monoaminooxidases (Georgotas *et al.* 1986; Halliwell, 2006), deficiency of ROS scavengers, such as monoamines (Pandey, 1992) and increased glutaminergic transmission (Avshalumov & Rice, 2002; Hashimoto *et al.* 2007). Abundant evidence indicates the association of depression with inflammatory processes, accompanied by ROS production via many mechanisms both on the periphery and in the central nervous system (CNS) (Linnoila *et al.* 1983; Maes, 1995; Leonard, 2001; Winterbourn, 2002; Cathart, 2004; Prasad, 2004; Saud *et al.* 2005; Adibhatla & Hatche, 2006; Fialkow *et al.* 2006; Raison *et al.* 2006; Leonard, 2007; Adibhalta *et al.* 2008). Overproduction of H_2O_2, its insufficient neutralization, can result in neuronal damage. If H_2O_2 overproduction outweighs the potential for its elimination by antioxidative defense system, a reaction leading to production of much more active and toxic form such as $^{\cdot}OH$ takes place (Coyle & Puttfarcken, 1993). Additionally, the presence of large amounts of polyunsaturated fatty acids (PUFAs), important targets for ROS, in the brain should be emphasized (Halliwell, 2006). Evidence for increased ROS production in depression is provided by results of investigations indicating increased lipid peroxidation in depressive patients (Khanzode *et al.* 2003; Lucca *et al.* 2009). Overproduction of ROS is especially unfavorable in depression because they induce changes in cell membrane lipids, alter the omega3 to omega6 PUFAs ratios and cause loss of cell membrane fluidity (Peet *et al.* 1998). These changes lead to subsequent receptor damage and disturbances of normal serotoninergic and noradrenergic transmission (Maes & Smith, 1998).

For counteraction of the harmful effects of oxidative stress, the human organism is equipped with an active antioxidative defense system, consisting of antioxidative enzymes involved in ROS inactivation. These enzymes protect the cells against damage and apoptosis (Valko *et al.* 2007) and therefore they can be regarded as important protective elements in the pathogenesis of depression. This fact is significant taking into account decreased volumes of the hippocampus and prefrontal cortex due to inhibition of neurogenesis or enhanced apoptosis in these brain regions in the course of depression (Xu *et al.* 2006; Bachis *et al.* 2008).

Catalase (CAT) is one of the antioxidative enzymes. This enzyme, acting in cooperation with other ones, plays an integrating role in the first-line defense against oxidative stress. CAT is an enzyme containing heme in its structure. Its role is to control the cellular levels of H_2O_2 by its decomposition to water (H_2O) and oxygen (O_2) (Valko *et al.* 2007) particularly under oxidative stress conditions (Kinnula *et al.* 1992). CAT is a homotetramer of 220–230 kDa mass, encoded by a gene consisting of 13 exons separated from each other by 12 introns. The gene is localized on chromosome 11 (Quan *et al.* 1986), and that region is a candidate region for the development of mental disorders (Levinson *et al.* 1998). A few polymorphisms have been described for the catalase-encoding gene. Point mutation involving guanine substitution by adenine in intron 4 is a cause of splicing abnormality (Wen *et al.* 1990) whereas thymine deletion in exon 4 causes acatalasemia (Hirono *et al.* 1995). Polymorphism -844G>A is associated with development of hypertension (Jiang *et al.* 2001; Zhou *et al.* 2005). Genetic changes involving antioxidative enzymes can be responsible for changes of their activity and expression. One of known polymorphisms is substitution of cytosine with thymine in nucleotide 262 (-262C>T). The presence of such polymorphism affects transcriptional factor binding and causes increased baseline expression of CAT in various cell types as well as increased CAT level in erythrocytes. The presence of -262T allele is an element preventing neurodegeneration and impaired physical fitness. The presence of this allele is also associated with cognitive function improvement (Christiansen *et al.* 2004). Substitution of thymine for cytosine in nucleoctide 262 generates three genotypes. CC genotype is associated with a significant decrease of enzyme expression in comparison with genotypes TT and CT (Gavalas *et al.* 2006). The ethnic differences in polymorphism distribution are presented in ***Table 1***.

An increase of CAT activity is observed in inflammations and other diseases accompanied by oxidative stress (Al-Abrash *et al.* 2000). Studies assessing CAT activity in patients with depression, a disorder characterized by inflammatory components, inform about increased activity of this enzyme in comparison with healthy subjects (Szuster-Ciesielska *et al.* 2008; Lucca *et al.* 2009b).

Considering increased ROS generation in depression, reduction of depression-related brain areas, the

Table 1. Ethnic differences of the T-262C CAT polymorphism in healthy subjects

	Genotypes			**AF**
	C-*262*C *n (%)*	**C-*262*T** *n (%)*	**T-*262*T** *n (%)*	**-*262*C** *(%)*
Healthy individuals				
Polish (149) [present study]	74 (49.7%)	62 (41.6%)	13 (8.7%)	75.5
Polish (199) [53]	115 (58%)	73 (37%)	11 (5%)	76.1
Chinese (316) [39]	279 (90.6%)	CT+TT 29 (9.4%)		95.1
English (296) [18]	120 (72.3%)	46 (27.7%)	0 (0%)	87.6
Afro-American [10]	120 (90.8%)	11 (9.2%)	0 (0%)	95.4

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role of CAT in inflammatory diseases and protection against apoptosis, as well as research results indicating changes in CAT activity in depressive patients, it was undertaken to assess whether there is a correlation between the risk of development of recurrent DD and -262C>T CAT polymorphism.

The catalase-encoding gene can be one of the candidates for susceptibility to the development of depression, and individual antioxidative potential might result from polymorphism of the genes encoding antioxidative enzymes (Forsberg *et al.* 2001).

MATERIAL AND METHODS

Patients

The study enrolled 149 patients treated for recurrent DD. The diagnosis was established according to ICD-10 criteria (F33.0 – F33.8) (World Health Organization, 1992). Subjects with other psychiatric diagnoses concerning axis I and II disorders were excluded from the study. In all included cases, the history was taken using standardized Composite International Diagnostic Interview (CIDI) (World Health Organization, 1992). Additionally, the number of depression episodes, duration of the disease and age at onset was assessed in each patient. Malignant tumors and serious neurological disorders were the exclusion criteria.

The control group consisted of 149 healthy subjects with family history negative for psychiatric disorders. Like in the study group, subjects with neurological disorders and malignancies were excluded. All the patients and control subjects were native, unrelated Poles, inhabitant of central Poland. Informed consent was obtained from all the participants of the study, which was approved by the local Bioethics Committee No RNN/566/08/KB.

Methods

Genomic DNA was extracted from whole blood samples according to the GTC method (Chomczynski, 1993). DNA encoding the promoter region of the CAT gene containing a -262 C-T substitution was amplified by polymerase chain reaction (PCR) using 0.1 μg genomic DNA, 200 μM each dNTP, 5x GoTaq buffer solution, 1u GoTaq polymerase (Promega, Madison WI USA), 0.5 μM CAT primers 5' AGAGCCTCGCCCCGCCGGACCG3' and 5' TAAGAGCTGAGAAAGCATAGCT 3'. After a 5 min denaturing step amplification was performed according to the following cycling profile: 94 °C for 30 sec, 68 °C for 30 sec and 72 °C for 30 sec (19 cycles) than 94 °C for 30 sec, 58 °C for 30 sec, 72 °C for 30 sec, 25 times. The final elongation step was 10 min at 72 °C. Amplification product 185 bp was digested with restriction enzyme SmaI. The polymorphism was visualized by separating the digested amplification products on 6% polyacrylamide gel. The -262T allele produced an undigested product of 185 bp, -262C allele two products: 155 bp and 30 bp.

Statistics

Statistical analysis of the collected material utilized descriptive methods as well as statistical conclusion. In order to describe the studied group of patients and the control group, structural indexes were calculated in qualitative analysis of characteristics. To estimate the average values for quantitative characteristics, arithmetic means ($\bar{x}$) i medians (Me) were calculated. Standard deviation (SD) was adopted as a measure of scatter of the results. Comparisons between the groups for data expressed as proportions were assessed with Chi^2 independence test (χ^2) for four- and r x c- field tables. For all analyses, the maximum acceptable type I error (i.e. true zero hypothesis rejection) probability value was set at α=0.05. Odds ratio of the disease (OR_{dis}) was calculated, depending on the observed parameter, according to Bland and Altman (2000).

RESULTS

The study was carried out on a group of 149 patients treated for recurrent DD (91 women – 61.07% and 58 men – 38.93%). The control group consisted of 149 subjects (83 women – 55.7% and 66 men – 44.3%). There were no statistically significant differences in age and gender in both groups (p>0.05). Genotype distribution in the control group (CG) and in the patient group (DD) was consistent with Hardy and Weinberg distribution for the assessed -262C>T polymorphism (DD: χ^2–6.98^{E-6} ; CG: χ^2–0.173).

Genotype distribution and allele frequency for the assessed polymorphism in CG and DD with gender subgroups and statistical analysis are presented in ***Tables 2 and 3***, respectively. No statistically significant differences in genotype distribution and allele frequency were observed.

Table 4 presents distribution of –C and –T alleles as well as odds ratio of diseases in relation to the presence of –C allele or C-262C homozygote in the CAT gene in the whole population or in gender subgroups. The remaining genotypes were treated as one group (T-262T + C-262T) in calculation of OR_{dis} for the presence of C-262C homozygote.

No statistically significant differences in genotype distribution and allele frequency related to sociomedical characteristics were observed either in CG or in DD. Statistical analysis concerning the correlations for the age at onset, duration of the disease and number of episodes in the DD group is presented in ***Table 5.***

DISCUSSION

Our study is the first one to assess the correlation between the risk of developing DD and the functional polymorphism of the single nucleotide -262-C>T in the gene encoding CAT, the enzyme involved in the first-line defense against ROS. The analyzed polymorphism affects expression and activity of CAT depending on

Table 2. The genotype distributions in the T-262C CAT polymorphism in DD and CG with statistical analysis

	C-*262*C *n (%)*	**C-*262*T** *n (%)*	**T-*262*T** *n (%)*	***p* value**
DD females n=91	42 (46.2%)	41 (45.1%)	8 (8.8%)	*p*=0.879
CG females n=83	41 (49.4%)	36 (43.4%)	6 (7.2%)	
DD males n=58	32 (55.2%)	21 (36.2%)	5 (8.6%)	*p*=0.296
CG males n=66	43 (65.2%)	21 (31.8%)	2 (3.0%)	
DD whole sample n=149	74 (49.7%)	62 (41.6%)	13 (8.7%)	*p*=0.359
CG whole sample n= 149	84 (56.4%)	57 (38.3%)	8 (5.4%)	

Table 3. Alleles distributions in the T-262C CAT polymorphism in DD and CG with statistical analysis

	DD n (%)	CG n (%)	*p* value
-5777C	210 (70.5)	225 (75.5)	*p*=0.16 df=1 X^2=1.91
-5777T	88 (29.5)	73 (24.5)	

Table 4. Alleles distributions in the T-262C CAT polymorphism in DD and CG with the value odds ratio of diseases for allele -262C and homozygote C-262C

	-262C *n (%)*	OR_{dis} for -262C; 95% CI	**C-262C *n (%)***	OR_{dis} for C-262C; 95% CI
DD females n=182	125 (68.7%)	0.89 0.56-1.41	42 (46.2%)	1.03; 0.62-1.71
CG females n=166	118 (77.1%)		41 (49.4%)	
DD males n=116	85 (73.7%)	0.64 0.35-1.67	32 (55.2%)	0.67; 0.39-1.14
CG males n=132	107 (81.1%)		43 (65.2%)	
DD whole sample n=298	210 (70.5%)	0.77 0.53-1.11	74 (49.7%)	0.76; 0.48-1.2
CG whole sample n= 298	225 (75.5%)		84 (56.4%)	

Table 5. Correlations between selected clinical features of recurrent depressive disorder and distribution of T-262C CAT genotypes in the DD patient group

	Rozkład genotypów T-262C CAT w grupie pacjentów DD
Age at onset (years)	H=1.571; p=0.456
Duration of the disease (years)	H=1.142; p=0.564
Number of episodes	H=1.754; p=0.415

the genotype present. Progressive genotype-related decrease of CAT activity from TT , through CT to CC genotype was observed (Forsberg *et al.* 2001).

The obtained results inform about no correlation between the risk of depression and genotype distribution and allele frequency in -262C>T polymorphism of the CAT gene. The presence of -262C>T polymorphism shows no correlations with the age at onset, duration of the disease , number of episodes and the patient's gender. Results indicating no correlation between the analyzed CAT gene polymorphism and the risk of disease was demonstrated also for Alzheimer's disease (AD) (Goulas et al., 2002; Capruso *et al.* 2008). The data obtained by these investigators inform about no significant correlation between genotype distribution and allele frequency both in the patients and the control group. This fact is important in view of clinical evidence that depression is an element preceding the onset of AD and can occur as its early symptom. It should be emphasized that both depression and AD are characterized by the presence of inflammatory components, manifested, among others, by increased activity of macrophages in the blood and microglial cells in the brain (Leonard, 2007). No correlation with the presence of -262C>T polymorphism was also demonstrated in diseases of inflammatory etiology, in which oxidative stress plays an important role and which are accompanied by depression (Katon *et al.* 2007). Such results were obtained in a study by El-Sohemy et. al. (2000), on a group of subjects of Asian origin with rheumatoid arthritis (RA), an inflammatory disease that often coincides with depression. Another disease in which oxidative stress and inflammatory

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processes play an important role, and which coincides with depression, is systemic lupus erythematosus (SLE) (Nery *et al.* 2007). The results based on a study of Asian population presented by Eny *et al.* (2005) also demonstrate no correlation between the risk of developing SLE and -262C>T polymorphism. On the other hand, correlation between CC genotype associated with reduced CAT activity and some of the clinical symptoms of SLE was demonstrated in Polish population. Nevertheless, this correlation was not associated with the risk of the disease (Warchoł *et al.* 2008). It should also be emphasized that the presence of inflammatory components in DD patients is detected in the subjects with no diagnosed inflammatory processes of known etiology. Therefore, it is important to elucidate the correlation between the risk of depression and the polymorphism of CAT affecting the activity of the enzyme.

There are reports informing about increased activity of CAT, both peripheral and in the CNS, observed in patients with depression (Szuster-Ciesielska *et al.* 2008; Lucca *et al.* 2009b). Free radical processes in depression are confirmed by increased production of superoxide anion radical (Lucca *et al.* 2009b), whose dismutation by superoxide dismutases (SOD) leads to generation of H_2O_2 (Valko *et al.* 2007). No correlation between the analyzed CAT polymorphism and an increase in CAT activity observed by many investigators might indicate that this increase can be stimulated by factors independent of the genotype, such as proinflammatory cytokines (Gurgul *et al.* 2004). Antidepressants influence the increase in expression of antioxidative enzymes as well (Li *et al.* 2000). Taking into consideration the study carried out by Tate *et al.* (1995), an increase of CAT activity induced by H_2O_2 alone can be expected , as there are a number of processes in depression leading to H_2O_2 production. Increase of CAT activity independent of genotype has been observed in chronic obstructive pulmonary disease (COPD) (Mak *et al.* 2007) and asthma (Mak *et al.* 2006). It is especially important that CAT activity increase in asthma was observed in Asian population, in which the T allele playing a protective role in this disease is rare (Mak *et al.* 2006) It should be emphasized again that the aforementioned diseases are characterized by inflammatory elements and oxidative stress. Additionally, they often coincide with depression (Katon *et al.* 2007).

The lack of correlation between the risk of DD and the analyzed polymorphism may result from no expected expression of the CAT gene in brain cells. It is not known whether the investigated polymorphism exerts any influence on increasing CAT expression in the brain, and even if it has, to what extent and whether it affects CAT expression in the brain regions associated with the development of DD. Additionally, even the presence of the analyzed polymorphism determining increased CAT expression and activity in brain cells may not play an important role in ROS neutralization and development of DD, as CAT occurs in the brain in small amounts (Halliwell, 2006). Moreover, even the presence of 262C>T polymorphism does not guarantee increased activity because of the possibility of CAT occurrence in the inactive mono- or dimeric forms instead of active tetrameric one (Wiemer *et al.* 1992).

Our study has demonstrated no correlation between -262C>T polymorphism and the risk of development of DD. However, taking into consideration the processes inducing oxidative stress in depression, further studies assessing correlations between the risk of DD and polymorphism of antioxidative enzymes should be undertaken, addressing ethnic differences and size of the studied populations. In view of the studies demonstrating the role of oxidative stress in DD, polymorphism of the CAT gene and genes encoding antioxidative enzymes can be the candidate sites associated with susceptibility to depression. The family of such enzymes includes glutathione peroxidases, acting in cooperation with glutathione reductase (Dringen *et al.* 2005; Valko *et al.* 2007). Peroxyredoxins, regarded as important free radical scavengers in the CNS, play also an important role in elimination of H_2O_2 in brain cells (Hattori & Oikawa, 2007).

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