

Review Article

Human Catalase, Its Polymorphisms, Regulation and Changes of Its Activity in Different Diseases

(catalase / oxidative stress / polymorphisms / gene expression)

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Abstract. Catalase (CAT) is a well-studied enzyme that plays an important role in protecting cells against the toxic effects of hydrogen peroxide. In human, it has been implicated in different physiological and pathological conditions. This review summarizes the information available on the function and role of CAT polymorphisms in pathogenesis of various pathophysiological states as well as on the regulation of CAT gene expression. Numerous studies have described the CAT polymorphisms and their link with various diseases. Changes in the CAT levels were reported in many different diseases and polymorphisms in the CAT gene were shown to be associated with different pathophysiological states, e.g. hypertension, diabetes mellitus, insulin resistance, dyslipidaemia, asthma, bone metabolism or vitiligo. Regulation of the CAT gene expression plays an important role in the levels of CAT. The catalase gene expression is regulated by various mechanisms involving e.g. peroxisome proliferator-activated receptor γ

(PPAR γ), tumour necrosis factor α (TNF- α), p53 protein and hypermethylation of CpG islands in the catalase promoter. Transcription of the CAT gene is mainly influenced by the -262 C/T and -844 A/G polymorphisms. A common polymorphism -262 C/T in the promoter region has been found to be associated with altered CAT activities. Apart from genetic factors, the activities of CAT may be affected by age, seasonal variations, physical activity, or a number of chemical compounds. Future investigations are necessary to elucidate the role of CAT in pathogenesis of oxidative stress-related diseases.

Introduction

Catalases (CAT, H₂O₂ : H₂O₂ – oxidoreductase, EC: 1.11.1.6) are enzymes with a long history that goes back to the 19th century, when they became one of the first sources of valuable information about the nature and behaviour of enzymes (Zámocký and Koller, 1999). The name catalase was given to the enzyme in 1900 owing to its catalytic action on hydrogen peroxide (Loew, 1900). Human catalase belongs to the group of monofunctional haem-containing catalases; members of this large subgroup are found in almost all aerobically respiring organisms (Zámocký and Koller, 1999; Chelikani et al., 2004). Catalase is primarily an intracellular enzyme; its highest concentrations in mammals are found in erythrocytes and liver and occasionally in the kidney (Deisseroth and Dounce, 1970). In tissues such as liver, catalase is found predominantly in peroxisomes (Quan et al., 1986).

Catalase is a tetrameric protein of 244 kDa with molecular 222 symmetry, comprising four identical subunits of 59.7 kDa. Each subunit contains 527 amino acid residues, one haem group, namely iron (III) protoporphyrin IX, and a tightly bound molecule of NADPH (Kirkman and Gaetani, 1984, 2007; Ko et al., 2000; Safo et al., 2001). Under physiological conditions erythrocytes contain 1.31–2.71 μ g CAT/mg Hb. These values correspond to an expected concentration of 6.6 to 13.7 μ M for catalase-bound NADPH in human erythrocytes (Kirkman and Gaetani, 1984). The exact role and

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Abbreviations: Ang II – angiotensin II, CAT – catalase, CP – chronic pancreatitis, DM1, 2 – diabetes mellitus, GPX – glutathione peroxidases, HCC – hepatocellular carcinoma, MetS – metabolic syndrome, NF- κ B – nuclear factor κ B, NOX – NADPH oxidases, PAX-6 – paired box 6, PIG3 – p53-inducible gene 3, PPRE – PPAR γ response element γ , PPAR γ – peroxisome proliferator-activated receptor γ , ROS – reactive oxygen species, SARS – severe acute respiratory syndrome, SBP – systemic blood pressure, siRNA – small-interfering RNA, SIRS – systemic inflammatory response syndrome, TGF- β – transforming growth factor β , TNF- α – tumour necrosis factor α .

function of NADPH in catalase was discussed in various reports (Kirkman et al., 1987; Hillar and Nichols, 1992; Almarsson et al., 1993; Olson and Bruice, 1995; Kirkman et al., 1999; Rovira 2005; Kirkman and Gaetani, 2007) and it was estimated that NADPH prevents formation of the inactive form of CAT (iron (IV) oxo-protoporphyrin IX) and also mildly increases the rate of removal of this inactive form; thus, NADPH protects CAT against inactivation by H_2O_2 (Kirkman et al., 1987, 1999).

The main function of catalase is decomposition of hydrogen peroxide to water and oxygen – catalatic activity. During long-term exposure of CAT to H_2O_2 , the catalase-bound NADPH became oxidized to $NADP^+$ and the activity of CAT fell to about one-third of the initial activity (Kirkman et al., 1987). In addition to a very efficient catalatic reaction mode, catalase could also catalyse 2-electron peroxidations of short-chain aliphatic alcohols at reasonable rates (Zámocký and Koller, 1999). The catalatic reaction predominates when the H_2O_2 concentration is higher than 10^{-4} M, while below this concentration in the presence of an acceptable hydrogen donor the peroxidatic reaction dominates (Maté et al., 1999).

It is known that H_2O_2 may play a key role in human physiological and pathophysiological processes. It is an important “second messenger” and signalling molecule at the cellular level. One of the main sources of reactive oxygen species are NADPH oxidases (NOX) that primarily produce superoxide, which is rapidly dismutated to H_2O_2 by superoxide dismutase. It has been shown that conditions in which NOX4 primarily generates superoxide lead to activation of proinflammatory transcription factors, and of stress-signalling pathways through mitogen-activated protein kinases, accumulation of Ca^{2+} , and decreased NO availability, which is linked to vascular inflammation and endothelial dysfunction. On the other hand, direct generation of H_2O_2 by NOX4 leads to signalling pathways that promote vasodilatation and cell protection (Touyz and Montezano, 2012).

In vivo, there are three families of enzymes which could remove hydrogen peroxides: catalases, glutathione peroxidases (GPX) and peroxiredoxins. Catalase may be the key enzyme for H_2O_2 removal in peroxisomes, although peroxiredoxin 5 may also contribute. At low H_2O_2 concentrations, GPX1 and peroxiredoxins are responsible for its degradation. Although peroxiredoxins are slower at catalysing H_2O_2 degradation than

GPX1, it has been suggested that at low H_2O_2 concentrations, peroxiredoxins dispose of most H_2O_2 generated inside cells. Catalase plays an important role in removing higher intracellular H_2O_2 concentrations (Halliwell and Gutteridge, 2007).

In 2003 Heck et al. discovered that in keratinocytes CAT could generate reactive oxygen species (ROS) in response to UVB light. The ability of the enzyme to generate ROS was dependent on the dose of UVB light utilized and the concentration of CAT (Heck et al., 2003). Therefore, Chelikani et al. (2004) speculated that the NADPH cofactor could have a role in ROS generation. These results implicate another role for NADPH in the catalase physiology.

In this review we try to elucidate the link between catalase polymorphisms and its activity in different diseases. The second important point of this review is to summarize findings about the catalase activity regulation.

1. Gene characteristics

The isolation and characterization of the human catalase gene were done in 1986 by Quan et al. (1986). The gene for human catalase has been mapped to chromosome 11, band p13, and is split into 13 exons by 12 introns and spans (Quan et al., 1986). Numerous polymorphisms have been described in the promoter, 5' and 3'- untranslated regions, exons and introns (Fig. 1). More precisely, the *CAT* gene is located from base pair 34,460,471 to base pair 34,493,606 on chromosome 11 (<http://ghr.nlm.nih.gov/gene/CAT#location>). The gene was shown to have eight initiation points of transcription, three CCAAT boxes, and three GC-like boxes, but to lack a TATA box and an initiator consensus sequence in the promoter region, which leads to multiple start sites of transcription (Sato et al., 1992; Toda et al., 1997).

2. Polymorphisms

In 2012, 245 catalase single-nucleotide polymorphisms were detected and described according to the NCBI database in different regions of the *CAT* gene (Crawford et al., 2012a). Significant correlations of the studied polymorphisms and various diseases are presented in Table 1. It has been shown that genetic variations in the *CAT* gene and its promoter may play a role in glucose disorders and may be risk factors for meta-

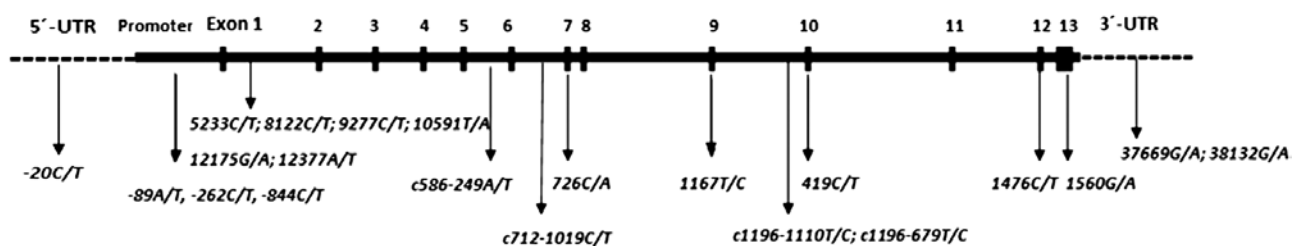


Fig 1. *CAT* gene and relevant single-nucleotide polymorphisms

UTR – untranslated region. Arrows correspond to catalase gene introns and exons. Source: Liu et al. (2010); Hebert-Schuster et al. (2012)

Table 1. Studied *CAT* gene single-nucleotide polymorphisms and their associated diseases

Polymorphism (NCBI ref. SNP ID)	Region of gene	Disease	Reference	Findings
-844C/T or -844G/A (rs769214)	Promoter	Hypertension Malnutrition Asthma	Jiang (2001) Watanabe (2010) Fabre (2008) Hebert-Schuster (2011) Podgoreanu (2006)	TT genotype is associated with increased SBP Independently predicted risk of progression of hypertension A allele is associated with lower renutrition efficiency A allele is associated with lower renutrition efficiency CT genotype is associated with postoperative myocardial infarction
-262C/T or 330C/T (rs1001179)	Promoter	Type 1 diabetes Breast cancer Hepatocellular carcinoma (HCC) Rheumatoid arthritis Asthma Ulcerative colitis Asbestosis Hyperkeratosis Various	Chistiakov (2004) Chistiakov (2006) Ahn (2005) Quick (2008) Ahn (2006b) Ezzikouri (2010) Grabar (2009) Mak (2006) Islam (2008) Khodayari (2013) Franko (2008) Ahsan (2003) Christiansen (2004)	CC genotype represented higher DMI risk C allele is associated with higher DMI risk T allele is associated with increased breast cancer risk T allele is associated with increased breast cancer risk in non-Caucasians, no significant association in Caucasians CC genotype is associated with decreased breast cancer risk TT genotype had increased risk to develop HCC T allele is associated with lower activity of rheumatoid arthritis T allele is associated with decreased risk of asthma in non-smokers T allele is associated with increased risk of asthma among Hispanic children, not in non-Hispanic white children CT genotype is associated with increased risk of ulcerative colitis TT genotype is slightly associated with elevated risk of asbestosis CT/TT genotype is associated with increased risk of arsenic-induced hyperkeratosis T allele is associated with improved physical functioning
-89A/T or -21A/T (rs7943316 rs17880664)	Promoter	Asthma Osteonecrosis Vitiligo	Polonikov (2009) Kim (2008) Liu (2010)	AA genotype is associated with increased risk of asthma T allele is associated with protective effect on osteonecrosis T allele is associated with increased risk of vitiligo
-20C/T (rs1049982 rs17881315)	5'UTR	Hypertension Osteonecrosis	Mansego (2011) Kim (2008)	T allele is associated with lower blood pressure TT genotype is associated with increased risk of osteonecrosis
1167C/T; 389C/T, 22348 C/T; 111C/T; 389Asp/ Asp (rs769217 or rs17880449)	Exon 9 Codon 389	Type 1 diabetes Type 2 diabetes Vitiligo Osteonecrosis Bone mineral density	Tarnai (2007) Chistiakov (2004) Chistiakov (2000) Gavalas (2006) Kim (2008) Oh (2007)	T allele is associated with increased risk of diabetes mellitus 1 CC genotype is associated with increased risk of diabetes mellitus 1 T allele is associated with increased risk of vitiligo TT genotype is associated with increased risk of osteonecrosis T allele is associated with higher bone mineral density
5233C/T, c66+78C/T; +144C/T (rs10836235 or rs17886119)	Intron 1	Various	Rajic (2009)	CC genotype is associated with late cardiac toxicity in patients treated with anthracycline due to acute leukaemia in childhood
8122T/C, 3033C/T; c66+296T/C (rs525938)	Intron 1	Osteonecrosis	Kim (2008)	CC genotype is associated with increased risk of osteonecrosis
19628A/T, 14539A/T; c586-249A/T (rs3758730)	Intron 5	Osteonecrosis	Kim (2008)	TT genotype is associated with increased risk of osteonecrosis
29502T/C, 24413T/C; c1196-679T/C (rs2284365)	Intron 9	Osteonecrosis	Kim (2008)	CC genotype is associated with increased risk of osteonecrosis

bolic diseases such as impaired glucose tolerance, insulin resistance, diabetes mellitus, hypertension, dyslipidaemia and osteoporosis and their comorbidities (Hebert-Schuster et al., 2012). Additionally discovered polymorphisms are mapped in the gene card (http://www.genecards.org/cgi-bin/carddisp.pl?id=847&id_type=entrezgene).

2.1. Polymorphisms in the promoter region

2.1.1. Polymorphism -262C/T

In the promoter region of the *CAT* gene there is a common polymorphism of C to T substitution at position -262 (db SNP ID: rs1001179). This polymorphism may influence *CAT* transcription by modulation of the transcriptional factor binding position and increased ba-

sal *CAT* expression in various cell types as well as the *CAT* level in erythrocytes (Forsberg et al., 2001; Galecki et al., 2009a, Hebert-Schuster et al., 2012). The relationship between the -262C/T polymorphism and catalase concentration in whole blood was demonstrated by Forsberg et al. (2001). Carriers of the less common -262T allele display higher *CAT* levels compared to CC homozygotes (wild type) (Forsberg et al., 2001). Other authors described the association between the -262C/T *CAT* polymorphism and *CAT* activity. It was shown that CC homozygotes had higher activity of *CAT* compared to those with CT or TT genotype (Ahn et al., 2005, 2006b; Nadif et al., 2005; Perianayagam et al., 2007). Conversely, in the study of Mak et al. (2007) no association between the *CAT* -262C/T polymorphism and *CAT*

activity was observed. The presence of the -262 T allele prevents neurodegeneration and impaired physical fitness, and was associated with cognitive function improvement (Christiansen et al., 2004; Galecki et al., 2009a). Carriers of the CC genotype were observed to be the most frequent (Christiansen et al., 2004).

This polymorphism has been studied in different populations as well as in different pathophysiological states. No statistically significant differences were found in -262C/T genotype frequencies between controls and patients with systemic lupus erythematosus (Eny et al., 2005; D'Souza, 2008; Warchol et al., 2008; Ghaly et al., 2012), vitiligo (Gavalas et al., 2006; Kósa et al., 2012), pseudoxanthoma elasticum (Zarbock et al., 2007), Alzheimer's disease (Goulas et al., 2002; Capurso et al., 2008), schizophrenia (Boškovič et al., 2013), pancreatic cancer (Tang et al., 2010), prostate cancer (Choi et al., 2007), lung cancer (Ho et al., 2006), colorectal cancer (Funke et al., 2009b), cleft lip/palate-affected pregnancies (Mostowska et al., 2007), non-Hodgkin's lymphoma (Lightfoot et al., 2006; Farawela et al., 2012), hypertension (Hsueh et al., 2005; Zhou et al., 2005), chronic obstructive pulmonary disease (Mak et al., 2007), instant restenosis (Shuvalova et al., 2012) or bronchial asthma (Polonikov et al., 2009).

No association was found between the -262C/T *CAT* polymorphism and hepatocellular carcinoma in cirrhosis (Nahon et al., 2009), adult brain tumours (Rajaraman et al., 2008; Bhatti et al., 2009), chronic kidney disease and its progression (Crawford et al., 2012b), appearance of precancerous changes in the gastric mucosa (Steenport et al., 2007), depressive disorder (Galecki et al., 2009a, b) or adverse outcomes in acute renal failure (Perianayagam et al., 2007).

The study of Rajić et al. (2009) estimates no correlation between this polymorphism and late cardiotoxicity in patients treated for acute leukaemia in childhood. In the study by Funke et al. (2009a), no association of the *CAT* -262C/T polymorphism with survival in rectal cancer patients who received radiotherapy was observed. Similarly, in the study by Koistinen et al. (2006), no associations between the *CAT* -262C/T polymorphism and the overall survival of patients with acute myeloid leukaemia were found.

On the contrary, Ezzikouri et al. (2010) found that patients with the *CAT* TT genotype had 3.41-fold increased risk of hepatocellular carcinoma and reduced *CAT* activity.

In a Russian population, Chistiakov et al. (2004, 2006) have found significant association of polymorphism *CAT* -262C/T with diabetes mellitus type 1 (DM1); whereas the C allele and the CC genotype represented higher risk of the disease. Other studies did not confirm the association between this polymorphism and DM1 (Pask et al., 2006) or DM2 (Szelestei et al., 2005; Dos Santos et al., 2006; Chen et al., 2012a).

An association was found between this polymorphism and breast cancer risk (Ahn et al., 2005); however, the studies of Quick et al. (2008) and Li et al. (2009)

did not find any association between the *CAT* -262C/T polymorphism and breast cancer. According to the studies of Ambrosone et al. (2005) and Ahn et al. (2006a), there were no associations between the -262C/T *CAT* polymorphism and the outcome after treatment for breast cancer.

In Hong-Kong Chinese population, Mak et al. (2006) have found that the C allele is significantly different between patients with asthma and controls. They also found a significant difference in the prevalence of catalase CC and combined CT and TT genotypes between the patients and controls. Islam et al. (2008) have reported an association of the *CAT* -262C/T variant with asthma in Hispanic-white children. Among Hispanic-white children, carriers of the T allele were at increased risk of new-onset asthma compared with children who were homozygous for common allele CC. Among non-Hispanic-white children this polymorphism was not associated with asthma risk. Wenten et al. (2009) did not find any association between the *CAT* -262C/T polymorphism and asthma status in white Hispanic and non-Hispanic subjects.

A correlation between the *CAT* -262C/T polymorphism and the disease activity was found in patients with rheumatoid arthritis (Grabar et al., 2009); however, in a previous study by El-Sohemy et al. (2006) no association was observed. An association was also observed between this polymorphism and delayed graft function of kidney allografts (Dutkiewicz et al., 2010).

2.1.2. Polymorphism -89A/T (-21A/T)

The next polymorphism examined in the promoter region of *CAT* was the -89A/T polymorphism (db SNP ID: rs7943316), also known as -21A/T. This polymorphism was studied in patients with DM (Ukkola et al., 2001; Nemoto et al., 2007; Flekac et al., 2008), asthma (Mak et al., 2006; Polonikov et al., 2009), chronic obstructive pulmonary disease (Young et al., 2006), hypertension (Jiang et al., 2001), osteonecrosis (Kim et al., 2008) and vitiligo (Park et al. 2006; Liu et al., 2010) and in patients after cardiac surgery (Podgoreanu et al., 2006).

No association was found between the -89A/T polymorphism and DM1 (Flekac et al., 2008), DM2 (Ukkola et al. 2001; Flekac et al. 2008), or diabetic nephropathy (Panduru et al., 2010) or coronary atherosclerosis in diabetic patients (Nemoto et al., 2007). No associations between hypertension (Jiang et al., 2001), chronic obstructive pulmonary disease (Young et al., 2006) and this polymorphism were observed.

In Russian population, Polonikov et al. (2009) found a significant difference in the distribution of genotypes of polymorphism -89A/T between patients with asthma and controls – the homozygous genotype -89AA was more frequent among asthmatics than among the controls. Mak et al. (2006) demonstrated no differences in genotype distribution between the patients with asthma and controls.

The results of the studies of vitiligo patients are also inconsistent. In Korean population no association be-

tween the *CAT* -89A/T polymorphism and vitiligo was demonstrated (Park et al., 2006), whereas Liu et al. (2010) observed association of AT and TT genotypes in Chinese population with increased vitiligo risk. According to the study of Kim et al. (2008), the T allele of -89A/T had a protective effect on osteonecrosis of the femoral head. In the study by Fabre et al. (2008), the -89A/T polymorphism was defined as a possible marker for predicting efficiency of renutrition. According to the study of Podgoreanu et al. (2006), the -89A/T polymorphism was not found to be a predictor of postoperative myocardial infarction in patients after cardiac surgery.

2.1.3. Polymorphism -844C/T

The third demonstrated polymorphism in the promoter region is -844C/T (db SNP ID: rs769214). This polymorphism may influence *CAT* transcription by modulation of the transcriptional factor binding position polymorphism (Hebert-Schuster et al., 2011, 2012). It has been shown that the T allele of the -844C/T polymorphism is associated with higher CAT activity in basal conditions, depending however on the binding site of transcriptional factor PAX6 (paired box 6). It has been shown that CAT is associated with transcription factor PAX6 that is involved in glucose homeostasis (Hebert-Schuster et al., 2011). In the presence of PAX6, this T allele is associated with decreased CAT activity in comparison with the C allele (Hebert-Schuster et al., 2012). Similarly, Nadif et al. (2005) found association of this polymorphism with CAT activity, when subjects with TT genotype had lower activity than those with CC genotype (Hebert-Schuster et al., 2012). According to the study of Yanping et al. (2004), carriers of the -844T variant had higher CAT transcriptional activity than carriers with the C variant.

Jiang et al. (2001) observed strong association of the -844C/T polymorphism with essential hypertension; these results are in accordance with Watanabe et al. (2010), whereas in the study of Zhou et al. (2005) this association was not confirmed. Islam et al. (2008) reported that there is a lack of association between -844C/T and risk of asthma. Similarly, Rajaraman et al. (2008) did not observe any association between this genotype and risk of some central nervous system tumours (such as glioma, glioblastoma, meningioma, and acoustic neuroma).

In the study of Fabre et al. (2008) the -844C/T polymorphism was specified as a promising marker for predicting efficiency of renutrition. *In silico* analysis has shown that the A allele of the polymorphism -844 A/G (commonly called -844C/T) carries a PAX6-binding site. PAX6 is required for differentiation of cells producing glucagon and thus important in glucagon biosynthesis. Fabre et al. (2008) found inefficient renutrition caused by the A allele of the *CAT* gene. Binding of PAX6 could modify transcription of *CAT* and thus influence glucagon secretion. It was shown that this polymorphism is an independent predictor of postoperative myocardial infarction in patients who underwent cardiac surgery (Podgoreanu et al., 2006).

2.2. Polymorphism -20C/T

In the 5'UTR region of the *CAT* gene, there is the well-described -20C/T polymorphism (db SNP ID: rs1049982). According to the study of Kim et al. (2008), this polymorphism is associated with osteonecrosis of the femoral head in the Korean population. In the study by Fabre et al. (2008) this polymorphism was defined as a possible marker for predicting efficiency of renutrition. In a larger genetic study the polymorphism -20C/T was associated with a risk of hypertension, when carriers of the T allele had decreased values of blood pressure (Mansego et al., 2011).

Other studies of this polymorphism did not show its association with essential hypertension (Jiang et al., 2001), bone mineral density and bone turnover markers (Oh et al., 2007), asthma status (Wenten et al., 2009) or with vitiligo (Casp et al., 2002).

2.3. Polymorphism 389C/T

Some polymorphisms were also detected in the exon regions of the *CAT* gene. Common polymorphisms are the 389C/T polymorphism of exon 9 (db SNP ID: rs769217), also marked as 1167C/T, 111C/T or 22348C/T, and the 419C/T polymorphism of exon 10 (db SNP ID: rs11032709). The study of Oh et al. (2007) indicates that the 389C/T polymorphism may be a useful genetic marker for bone metabolism. Carriers of the T allele had significantly higher bone mineral density and decreased osteocalcin levels. An association was also demonstrated between this polymorphism and the risk of osteonecrosis of the femoral head (Kim et al., 2008).

The 389C/T polymorphism was explored mainly in two diseases – vitiligo and diabetes mellitus. No difference in genotypes or allele frequencies between patients with vitiligo and controls was found in the studies by Casp et al. (2002), Liu et al. (2010), Shajil et al. (2007) and Park et al. (2006); the only studies that observed a difference in alleles and genotype frequencies was the study of Gavalas et al. (2006) and Lv et al. (2011). In vitiligo patients, an increased prevalence of the T allele was found in comparison with controls (Gavalas et al., 2006). Meta-analysis concerning the association between the 389 C/T polymorphism and the risk of vitiligo suggested that the CT genotype of the *CAT* gene is associated with an increased vitiligo risk and carriers with the T allele had higher risk of progressing vitiligo (Lv et al., 2011). Low CAT activity in vitiligo patients could be a result of the inhibitory effect of H₂O₂, or allelic variations in the *CAT* gene that may influence the expression of the enzyme or their function. Casp et al. (2002) reported that *CAT* mutations could lead to a risk of vitiligo by changes in the gene expression or structure in melanocytes and/ or keratinocytes.

The results of the studies focused on polymorphism 389C/T in patients with DM are not homogenous. The 389C/T polymorphism of *CAT* was associated with DM1 (Chistiakov et al., 2004; Tarnai et al., 2007) and also DM2 (Chistiakov et al., 2000), whereas Pask et al.

(2006) found no association between this polymorphism and diabetes mellitus type 1. Chistiakov et al. (2006) investigated the association between this polymorphism and diabetic neuropathy in patients with diabetes mellitus type 1 and found no significant association. No significant differences were found between complicated and uncomplicated hypertensive patients with diabetes mellitus type 2 with respect to the allelic or phenotypic distribution of the 389C/T polymorphism (Sergeeva et al., 2001).

The 419C/T polymorphism was examined in patients with vitiligo in comparison with controls and there was no difference in the frequency of alleles or genotypes between these two groups (Casp et al., 2002; Gavalas et al., 2006; Liu et al., 2010).

2.4. Inherited catalase deficiency – acatalasemia

The deficiency of catalase was for the first time described by Takahara and Miyamoto in Japanese population in 1948 (Góth, 2001a). Three main types of CAT deficiency have been distinguished – Japanese, Hungarian and Swiss. Catalase deficiency is an inherited disease; its inheritance pattern is autosomal recessive. The homozygous condition is called acatalasemia, the heterozygous condition is designated as hypocatalasemia (Ogata et al., 2008). The deficiencies in mammalian catalase were described in detail in reviews by Ogata et al. (2008) and Góth and Nagy (2013). Acatalasemia is characterized by clinical features such as oral infections, mouth ulcers and gangrene, as well as altered lipid and carbohydrate metabolism (Góth et al., 2004; Góth and Nagy, 2012).

Japanese acatalasemia has been classified into two subtypes, by splicing mutation (G to A substitution) in position 5 of intron 4 and frame-shift mutation (T deletion) in position 358 in exon 4 (Ogata et al., 2008). In the individuals with homozygous condition the CAT activity is less than 10 % of normal erythrocyte activity, the heterozygous individuals have approximately half of normal erythrocyte catalase activity (Góth, 2001a). Takahara described oral progressive gangrene in Japanese acatalasemic patients; this gangrene due to acatalasemia was called Takahara's disease (Ogata et al., 2008). This disease was not observed in other types of acatalasemia (Góth, 2001a) and the incidence of the disease in Japanese acatalasemic patients decreased significantly (Ogata et al., 2008).

There are four subtypes of Hungarian acatalasemia – type A is characterized by the frame-shift mutation (GA insertion) in position 138 of exon 2, type B is described as frame-shift mutation (G insertion) in position 79 of exon 2, type C is defined as splicing mutation (G to T substitution) in position 5 of intron 7, and type D is defined as coding region mutation (G to A substitution) in position 5 of exon 9 (Ogata et al., 2008). All these subtypes of Hungarian acatalasemia were described by Góth (2001a,b) and Góth et al. (2000, 2001, 2005).

3. Regulation of catalase gene expression

The regulation of *CAT* gene expression plays an important role in the levels of catalase. The expression is regulated at the transcription, post-transcription and post-translation levels (Nishikawa et al., 2009). It was shown that the *CAT* gene expression is regulated by peroxisome proliferator activated receptor γ (PPAR γ). PPAR γ is a ligand-activated transcription factor that controls expression of the *CAT* gene by binding to a distal PPAR γ response element (PPRE) in its promoter region (Okuno et al., 2010; Yang et al., 2011). Girmun et al. (2002) showed that PPAR γ ligands, in general thiazolidinediones (ciglitazone, rosiglitazone, pioglitazone), increase the catalase mRNA and activity, and this is mediated *via* a functional PPRE in the rat catalase promoter. It has been shown that PPAR γ binds the promoter of *CAT* to regulate its expression in endothelial cells. Current data demonstrate that *CAT* is a PPAR γ target gene. Way et al. (2001) recently demonstrated *in vivo* that a non-thiazolidinedione PPAR γ ligand can increase catalase expression in tissues that contain PPAR γ .

Chen et al. (2012b) investigated the cardioprotective role of PPAR γ activation with rosiglitazone and pioglitazone in rabbit newborn and adult hearts. Activation of PPAR γ with rosiglitazone regulates *CAT* expression in newborn heart, with over-expression of PPAR γ in newborn rabbit heart. Yang et al. (2011) found that angiotensin II (Ang II) inhibited CAT and PPAR γ protein and mRNA expression. Transfection with PPAR γ small-interfering RNA (siRNA) led to a reduction in *CAT* expression. PPAR γ ligands enhanced *CAT* expression and inhibited extracellular signal-regulated kinase 1/2 (ERK 1/2) activation. The authors have found that Ang II decreased *CAT* expression in a time-dependent manner after a transient increase. Specific activation of PPAR γ by ligands (15d-PGJ2 and pioglitazone) remarkably increased CAT protein and mRNA levels in fibroblasts and attenuated the decrease of CAT in response to Ang II.

In their study Min et al. (2010) observed that down-regulation of catalase is caused by hypermethylation of a CpG island in the catalase promoter during prolonged exposure to reactive oxygen species (ROS). In hepatocellular carcinoma cells, transcription factor Oct-1 binds to the catalase promoter and acts as an activator. Similarly, Quan et al. (2011) found that prolonged exposure to ROS down-regulates catalase expression by hypermethylation of CpG sites in the promoter. Transcription factor Oct-1 binds to the catalase promoter and acts as a transcriptional activator of the catalase gene. Reactive oxygen species regulates catalase not only by a direct mechanism, but also through the transcriptional activator Oct-1 (Quan et al., 2011). Catalase down-regulation and methylation of its promoter *via* ROS effect is reversible in HCC cells (Min et al., 2010). Min et al. (2010) also showed down-regulation of catalase expression both in hepatocellular carcinoma (HCC) cells and

in HCC tissues, thus confirming that exposure to ROS is associated with catalase down-regulation and methylation of *CAT* promoter during the HCC development.

Another mechanism by which catalase can be regulated is p53 protein and p53-inducible gene 3 (*PIG3*). In their study Kang et al. (2013) observed that p53 protein and *PIG3* repressed the catalase activity. They have also found that catalase activity is decreased when p53 protein is over-expressed. Similarly, ectopic expression of *PIG3* decreased the *CAT* activity and caused increased ROS production (Kang et al., 2013). Catalase-binding regions of p53 and *PIG3* are important for interaction with *CAT* and for the regulation of *CAT* activity and ROS levels. High levels of p53 protein and *PIG3* down-regulates the *CAT* activity especially in cells under severe genotoxic conditions. On the contrary, in the study of Hussain et al. (2004), no effects of p53 on the expression of catalase protein were found. Strong *CAT* down-regulation at the protein level was shown in a liver cancer cell line by Ngoka (2008). This down-regulation is probably caused by genetic reprogramming in favour of increased proliferation of the cancer cells (Ngoka, 2008). Down-regulation of antioxidant enzymes is determinant in the process of neoplastic transformation of cells (St Clair et al., 1992). Some hypotheses for *CAT* deficiency in tumours and cancer cells have been proposed, such as hypermethylation of the *CAT* promoter or implication of transcription factors (Glorieux et al., 2011). Cancer cells are rapidly proliferating cells that produce increased H_2O_2 levels and had strongly decreased *CAT* activities in comparison with normal cells. Hydrogen peroxide functions as a second messenger of mitogenic signalling processes and stimulates cell proliferation, whereas *CAT* suppresses growth factor-dependent activation of MAPK and proliferation of cells. Signalling molecules PKA and PKC are involved in mitogenic signalling and could up-regulate the activity of catalase.

Catalase derivatives such as Gal-catalase (galactosylated) and Suc-catalase (succinylated) inhibited activation of nuclear factor κ B (NF- κ B) in liver and tumour cells and thus reduced metastases on the surface of the liver (Nishikawa et al., 2009). It has been shown that polyethylene glycol conjugate derivatives of *CAT* (PEG-catalase) inhibited early steps of tumour metastasis growth in the lung (Nishikawa et al., 2009). Catalase down-regulation was also shown to be caused by tumour necrosis factor (TNF- α) (Hebert-Schuster et al., 2011). Moreover, it has been shown that catalase expression is inhibited by transforming growth factor (TGF- β) in the airway smooth muscle cells of asthmatic and chronic obstructive pulmonary disease patients (Michaeloudes et al., 2011a,b).

Several studies have demonstrated that *CAT* gene expression could be stimulated by hydrogen peroxide (Tate et al., 1995; Lai et al., 1996) or by oxidized lipids (Meilhac et al., 2000).

4. Catalase activity in various diseases

The activities of *CAT* have been investigated in various pathophysiological states associated with increased oxidative stress. Decreased *CAT* activity was found in patients with diabetes mellitus type 1 (Twardowska-Sauchta et al., 1994; Atalay et al., 1997; Merzouk et al., 2003; Abou-Seif and Youssef, 2004) and in patients with DM2 (Kedziora-Kornatowska et al., 1998; Bhatia et al., 2003; Abou-Seif and Youssef, 2004; Komosińska-Vassev et al., 2005; Ramakrishna and Jaikhanani, 2008) in comparison to controls. In contrast, there are some studies showing increased activity of *CAT* in patients with DM1 (Gil-del Valle et al., 2005) and DM2 (Sözmen et al., 1999; Kesavulu et al., 2000, 2001; Sailaja et al., 2003). Activities of *CAT* were observed in patients with metabolic syndrome (MetS) with inconsistent results. Reduced *CAT* activity was observed in patients with MetS in comparison with healthy controls in the study of Koziróg et al. (2011) and Vávrová et al. (2013), whereas no difference in the *CAT* activity was observed in the studies of Broncel et al. (2010) and Pizent et al. (2010). Increased *CAT* activity was described by Cardona et al. (2008a,b). In patients with only one component of MetS – obesity (Viroonudomphol et al., 2000), hypertension (Rodrigo et al., 2007), or insulin resistance (Shin and Park, 2006) – a decrease in *CAT* activity was observed.

Increased *CAT* activities were found in patients with depressive disorders (Szuster-Ciesielska et al., 2008; Galecki et al., 2009a,b), multiple sclerosis (Miller et al., 2011) and bipolar disorder (de Sousa et al., 2014), whereas no differences in *CAT* activities were observed in depressive women (Kodydková et al., 2009) and patients with major depression (Bilici et al., 2001) compared to controls. Ozcan et al. (2004) described decreased *CAT* activities in erythrocytes of patients with affective disorders.

Observations of *CAT* activity in patients with various types of cancer are inconsistent. Casado et al. (1995) found decreased *CAT* levels in patients with lymphoma, breast cancer, head and neck cancer, gynaecological, and urological cancer. Increased *CAT* levels were found in patients with non-small cell lung cancer compared to controls (Tsao et al., 2007; Esme et al., 2008). Decreased *CAT* activity was reported in patients with prostate cancer (Arsova-Sarafinovska et al., 2009; Akinloye et al., 2009) and pancreatic carcinoma (Kodydkova et al., 2013).

The activity of catalase has also been investigated in patients with systemic inflammatory response syndrome (SIRS), sepsis, septic shock, or those suffering from severe acute respiratory syndrome (SARS). Increased *CAT* activity in patients with sepsis was reported by Warner et al. (1995), Leff et al. (1992, 1993) and Kapoor et al. (2006). In their study Leff et al. (1993) showed that patients with sepsis and ARDS had higher *CAT* activity than those without ARDS. Differences were observed in *CAT* activity between patients with ARDS and healthy

subjects (Metnitz et al., 1999). Some authors described decreased CAT activities in chronic pancreatitis (CP) (Quillot et al., 2005), whereas Szuster-Ciesielska et al. (2001a) found increased CAT activities in patients with CP compared to controls. No differences were observed in the studies of Fukui et al. (2004) and Kodydkova et al. (2013). Furthermore, it was shown that serum CAT was higher in patients with acute pancreatitis than in healthy controls (Góth et al., 1982, 1989; Szuster-Ciesielska et al., 2001; Fukui et al., 2004), whereas no significant differences were observed in erythrocyte CAT activity between patients with acute pancreatitis and control subjects in the study of Chmiel et al. (2002) and Vávrová et al. (2012).

5. Catalase activity and environmental factors

Apart from genetic factors, CAT activities are influenced by a number of environmental factors.

5.1. Catalase and age

Inconsistent results were reported in the studies investigating age-related changes of catalase. Liles et al. (1991) found an age-related decrease in catalase activity in human retinal pigment cells. This decrease could have resulted from a decrease in expression of catalase gene products, formation of inactive catalase complexes, or deficiencies in essential metal cations (e.g. iron, zinc and copper). Furthermore, Guemouri et al. (1991) showed only slightly diminished catalase activity in the elderly. Whereas Andersen et al. (1997) observed no age-related changes for CAT activity in erythrocytes, Jozwiak and Jasnowska (1985) described positive correlation of CAT activities with increased age.

5.2. Catalase and seasonal variations

In their study Balog et al. (2006) determined the effect of seasonal variation on the activity of catalase in a population of 12 trained subjects and age- and sex-matched sedentary controls. The authors observed seasonal variations in catalase in sedentary women; the lowest activity was observed in spring compared to the autumn and winter, and no seasonal variations were investigated in sedentary men. Some variations persisted in the trained women and men, but the season with lowest CAT activity in women was summer compared to autumn, whereas in trained men the CAT activity was decreased in autumn compared to spring. The seasonal variation in CAT activity could be explained by different levels of hormones such as melatonin, testosterone and oestradiol, and melatonin could up-regulate the antioxidant enzyme activity. Testosterone has pro-oxidant while oestradiol has antioxidant properties.

5.3. Catalase and physical activity

In the same study, Balog et al. (2006) determined the effect of sports on the activity of catalase. A difference in CAT activity was noticed between trained men and

trained women; women had usually higher CAT activity than men. In women sports had no effect, while in men sports decreased CAT activity in the autumn.

5.4. Catalase and chemical and physical influence

Catalase is sensitive to a number of substances that interact with the active site of the enzyme and inhibit the enzyme activity. Studies were focused on the effects of cyanide, azide, hydroxylamine, aminotriazole, S-ethylisothiosemicarbazide and mercaptoethanol on CAT activities (Margoliash et al., 1960; Switala and Loewen, 2002). Banerjee et al. (2010) found increased CAT activities in the serum of individuals with chronic arsenic exposure. They also found moderate positive correlation between arsenic concentration in urine and CAT activity in the serum.

A study of Lubkowska et al. (2009) has shown that single whole-body cryostimulation (-130 °C) in the course of 3 minutes resulted in a decrease of catalase activity in human erythrocytes measured 30 minutes after the low temperature challenge.

6. Conclusion

Catalase as one of the major antioxidant enzymes has been studied in a number of diseases associated with oxidative stress (e.g., atherosclerosis, hyperlipidaemia, diabetes mellitus, hypertension, and neurodegenerative diseases). Oxidative stress is implicated in the pathogenesis of these diseases. Catalase decomposes hydrogen peroxide generated by dismutation of superoxide catalysed by superoxide dismutase. Although it appears that increased CAT activities could be beneficial in the pathogenesis of atherosclerosis and metabolic diseases, the CAT role in pathogenesis of these diseases along with other enzymes degrading hydrogen peroxide (such as glutathione peroxidase and peroxiredoxins) and superoxide dismutase should be determined.

Further studies are required to elucidate the role of the *CAT* gene as a possible risk factor in the aetiology of oxidant-related diseases. Future investigations of the regulation of *CAT* gene expression could lead to new therapeutic approaches.

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