JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

ROLE OF CATALASE IN DIABETIC RETINOPATHY OF TYPE 2 DIABETES MELLITUS

[1]Akshi Valodara, [2]Kaid Johar SR

[1]PhD Student, [2]Associate Professor

[1,2] Department of Zoology, Biomedical Technology and Human Genetics, Gujarat University, Ahmedabad 380009, Gujarat, India

Abstract: Catalase is the most significant antioxidant enzymes and act as a main regulator of hydrogen peroxide (H2O2) mechanism against oxidative stress. It helps in maintaining essential biomolecules from getting damaged by oxidative stress. Catalase takes part in several biological mechanisms such as apoptosis, inflammation, tumour mutagenesis as well as endocrine system. Imbalance level of catalase enzyme, promoter polymorphism and deregulation of catalase (CAT) gene expression level is linked with diseases including diabetic retinopathy (DR) in type 2 diabetes mellitus (T2DM). This article discusses the role of altered level of CAT gene regulation, polymorphism in promoter region and its enzyme activity is associated with DR in T2DM development.

Keywords: Catalase, Oxidative stress, Type 2 diabetes, Diabetic retinopathy, Promoter polymorphism

1. Introduction

Catalase enzyme is heme-containing and found in all aerobic tissues in human. In bacteria and humans, it has been detected in various organs [1]. Catalase is essential antioxidant enzyme which naturally reduces oxidative stress by destroying hydrogen peroxide (H2O2), produces water (H2O) and oxygen (O2) [2]. There are no antioxidant enzymes with a higher turnover rate than catalase; as a molecule of this enzyme is capable of decomposing more than 1 million of H2O2 in a second [3]. An optimal pH range for catalases ranges from 5-10. 3-Amino-1, 2, 4-Triazole inhibits these glycoproteins, which do not respond well to organic solvents [4].

In the past and still today, H2O2 has been considered toxic for many types of organisms [5]. The human catalase enzyme (EC.1.11.16) playing a role in controlling H2O2 metabolism [1]. In addition to intracellular H2O2 levels, catalase appears to regulate extracellular H2O2 levels as well in red cells and may act as a protective mechanism against oxidative stress in other tissues [6]. Oxidative stress is caused when a balance is not maintained between generating and quenching reactive substance (free radicals such as RCS, ROS, RSS, RNS) [7]. As a result, important biomolecules lose functionality and become inflexible, which are two interdependent processes involves in the many pathological condition which cause numerous diseases. Catalase like most common antioxidant enzymes are helps in protecting such biomolecules (DNA, lipids, proteins and cellular components) from oxidative damage [8].

Several studies shows catalase activity was found to be higher in liver and kidney, lower in heart and brain while intermediate in lung and pancreases tissues [9, 10]. It is always the rate at which H2O2 is dissociated that determines the catalase activity [9]. Catalase is implicated in biological mechanisms in inflammation, apoptosis, stimulation of variety of tumors, mutagenesis as an influencing factor [11]. Different tissues are damaged by oxidants in different ways; catalase plays a role in antioxidant defence [12]. Moreover, functional polymorphism (SNPs) in the catalase promoter gene is associated with the development and progression of many disease including hypertension, type 2 diabetes mellitus (T2DM) and its complications, Alzheimer's disease, anaemia, cancer and Parkinson's disease. This review discusses about the role of catalase enzyme in the oxidative stress which cause

diabetes. Moreover, this article also highlight about role of PPARy in the catalase (CAT) gene regulation, its promoter polymorphism and altered level of enzyme is responsible for the generation of disease like T2DM and diabetic retinopathy (DR).

2. Structure

Numerous biochemical and molecular biology studies have focused on heme catalases because of its ubiquity and the availability of H2O2 and alkyl peroxides (substrates) [13]. With the aid of crystallography, several heme-containing monofunctional catalases have been solved, including those from bovine liver catalase (BLC) and animal erythrocytes (HEC), revealing that the core of this entire enzyme is highly conserved [14]. A number of crystal-growth experiments have utilized catalases due to their large molecular size. Human erythrocyte catalase (HEC) crystal structure has been determined. Three types of crystals were formed based on its purification and crystallization: hexagonal, tetragonal and orthorhombic [15]. Human catalase [EC.1.11.1.6] contains tetramers with subunits of about 60 kDa; there are 527 amino acid residues in each subunit and one heme group with Fe3+ [16]. Alanine (7.34%) is highly present in catalase than other amino acids and was found to play an influencing role in catalase composition [17]. In comparison with most other enzymes, tetrameric catalases are much more resistant to pH and thermal denaturation due to their rigid and stable structure [18]. Due to oxidative stress the function and structure of catalase enzyme gets deteriorate over a time in tissue and organ which cause diabetes.

3. Role of PPARy in CAT gene expression regulation

The CAT gene expression regulated at three levels: transcription, post-transcription and post translation level. Catalase enzyme production is controlled by gene expression [19]. CAT gene expression controlled by binding between peroxisome proliferator activated receptor y (PPARy) act as a ligand-activated transcription factor and PPRE (distal PPARy response element) in the promoter region [20, 21]. Study shown by Girnun et al. in human CAT promoter, PPARy ligand with ciglitazone, pioglitazone, rosiglitazone increase mRNA level while in rat promoter this process mediated by PPRE [22]. PPARy regulates CAT gene expression in endothelial cells. In oxidative stress condition, endothelial cells produce more H2O2 and O2 which enhance more generation of OH [23]. As a result endothelial dysfunction occure which further disturb the regulation of CAT gene expression level.

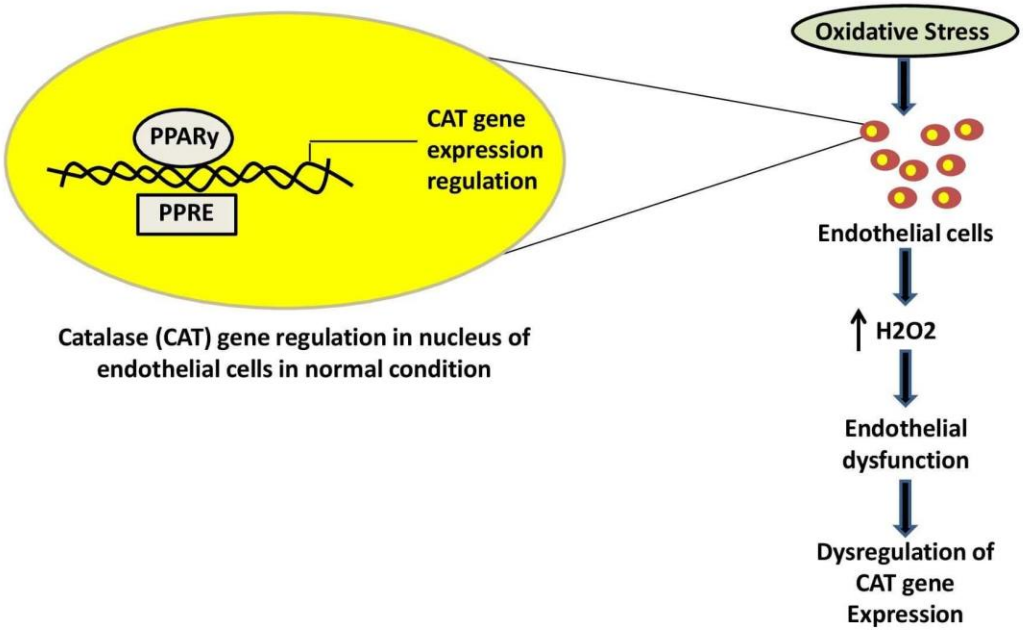

Figure 1: Oxidative stress makes endothelia cells dysfunctional and alters CAT gene expression.

4. Type 2 diabetes mellitus and complications

When glucose levels in blood are high, insulin is released and produced by β-cells of Langerhans islets. In T2DM people, β-cells are not able to produce sufficient insulin to maintain high glucose level (hyperglycemia) in blood and leads to β-cells dysfunction [23]. Progression of T2DM may be linked to a lack of proper regulation by catalase, an

antioxidant enzyme in the cells. Hence, the cells are likely to suffer oxidative damage because of this these prominent enzyme. In case of catalase deficiency, β-cells of pancreas undergo oxidative stress and produce more reactive oxygen species (ROS) that ultimate dysfunction β-cell and leads to T2DM [24]. In diabetes, especially those with poor glycemic control, reactive oxygen species are produced more frequently [25].

A significant part of diabetes related morbidity and mortality is attributable to the vascular complications. Alteration in production and elimination of H2O2 leads to development and progression of vascular complication in type2 diabetes [26]. A pivotal role in diabetic complications may be played by signalling pathways triggered by hyperglycemia, which produces ROS, leads to oxidative stress and cause cellular death [27]. Moreover, chronic life style and metabolic abnormality in T2DM patients also responsible for the development of various vascular complications. Microvascular conditions include neuropathy retinopathy and nephropathy while macrovascular conditions include ischemic heart disease and stroke, cerebrovascular complications. Both microvascular and macrovascular complications affects almost every part of an individual.

Moreover, Hyperglycemia is main important hallmark for microvascular disease [28]. Among all the microvascular conditions DR is the most common cause has been reported in many studies according to their prevalence in different ethnic groups. World-wide, DR remains the most common cause of blindness among working-age adults [29]. T2DM duration and severity of hyperglycemia linked with risk for the development of DR [30]. A complex mechanism governs the progression of DR. The process begins when hyperglycemia induces ischemia, some vasoactive chemicals like vascular endothelial growth factor (VEGF), which forms new blood vessels from the retina surface, and grows along with vitreous chamber on posterior wall. Newly formed blood vessels are fragile and are immature by nature, so they are susceptible to rapture. This leads to vitreous haemorrhages when blood and fluid leak out easily [31]. Vitreous detachments can occure as a consequence of a constricting vitreous, resulting in vision loss. Angiogenesis occurs during early stages of DR known as proliferative diabetic retinopathy and another subtype in the advance stage is non-proliferative diabetic retinopathy. DR strongly associated with connection between fluctuation in levels of antioxidant enzyme and poor glycemic control. Cell loses their function and integrity due to the attack of free radicals on cells leads to oxidative damage. Because of high amount of free radicals in cells, low level of antioxidant enzymes leads to cellular oxidation [32].

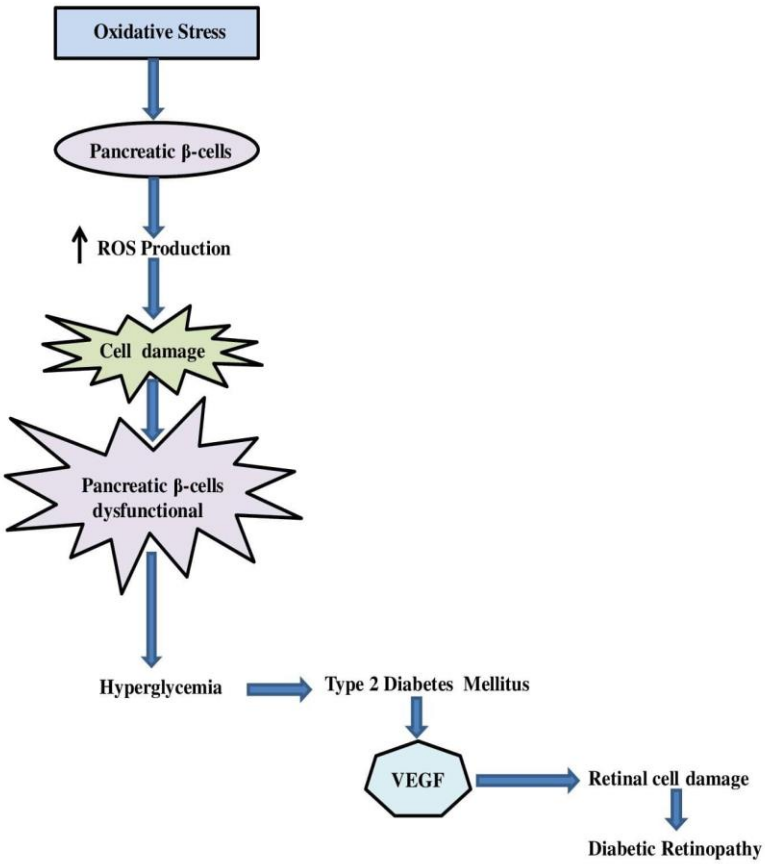

Figure 2: Excess reactive oxygen species leads to β-cells dysfunction in pancreas, and it further contributes in the development of diabetic retinopathy.

5. CAT gene and polymorphisms

In 1986, Quan et al. isolated and characterized the CAT gene from humans [33]. Human catalase (CAT, Gene ID: 847) resides on chromosome 13 at position 11 with 13 exons and 12 introns [34]. A more precise location of the CAT gene is between 34,460,471bp and 34,493,606bp on chromosome 11 [35]. Various SNPs have been identified in exons, introns, promoters, 5' and 3' untranslated regions. Several initiation points of transcription were shown for the gene, including three GC-like boxes and three CCAAT boxes, but the gene lacks an initiator consensus sequence and a TATA box in the promoter region, causing multiple transcription start points [34].

Promoter region playing a major role in the regulation of gene expression. Presence of polymorphism in the promoter region modifies binding sites of transcription factors (TFs) which alters the gene expression level. Affecting the gene expression level by functional promoter polymorphisms associated with diseases. Humans possess the most genetic polymorphism in the form of SNPs (single nucleotide polymorphisms) and they can affect gene function if they are located within or near a gene [36]. Polymorphisms (SNPs) in the promoter region of CAT gene are:-542 -/T (rs148068536), -533G/A (rs17883920), -330C/T (rs1001179), -254C/T (rs57470823), -21A/T or -89A/T (rs7943316), -20C/T (rs1049982) [37]. One of the most common polymorphisms, -21A/T (rs rs7943316) SNP located near a transcription start site (TSS). Study shows -21A/T is associated with DR in many ethnic groups. 21A/T polymorphism located in sensitive position and hence may alter the binding site of TFs. Misregulation of TFs deregulates the regulatory region where polymorphism resides. This ultimately disturbs to the mRNA and protein level in the disease condition.

6. Enzyme level in DR of T2DM

Numerous studies showed the link between benign polymorphisms of CAT gene in diabetic patients [38, 39] and low catalase activity leads to high H2O2 concentration in tissues and blood [40]. H2O2 at high concentration harm pancreatic β-cells (oxidative sensitive) resulting in law insulin production [41]. However it's still not clear the effect of H2O2 on insulin production or pancreatic function. There is a connection between high blood sugar and low antioxidant enzymes in T2DM condition. There are few papers available shows association between benign catalase polymorphism and low catalase activity. Decreased level of the catalase activity in DR of T2DM may be a result of an elevated enzymatic glycation due to high glucose level [42].

7. Conclusion

The pathogenesis of DR and T2DM is complicated because many factors are involved but studies from several laboratories have shown that catalase act as potential pathogen. Study shows eating food items that are high in antioxidants can reduce the risk T2DM and DR. A more in-depth examination of the activity and functional analysis of enzymes is warranted considering the importance of catalases. Using genetic data to make early diagnoses and develop new treatments may be possible.

References

1. Nandi, A., Yan, L. J., Jana, C. K. & Das, N. 2019. Role of catalase in oxidative stress-and age-associated degenerative diseases. Oxidative medicine and cellular longevity.
2. Kurutas, E. B. 2015. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutrition journal, 15(1): 1-22.
3. Smejkal, G. B. & Kakumanu, S. 2019. Enzymes and their turnover numbers. Expert Review of Proteomics, 16(7): 543-544.
4. Yumoto, I., Ichihashi, D., Iwata, H., Istokovics, A., Ichise, N., Matsuyama, H. & Kawasaki, K. 2000. Purification and characterization of a catalase from the facultatively psychrophilic bacterium Vibrio rumoiensis S-1T exhibiting high catalase activity. Journal of Bacteriology, 182(7): 1903-1909.
5. Yoon, H., Kim, H. C., Kim, J., You, K., Cho, Y. and Kim, S. 2022. Toxicity impact of hydrogen peroxide on the fate of zebrafish and antibiotic resistant bacteria. Journal of environmental management, 302: 114072.
6. Sies, H. 2014. Role of metabolic H2O2 generation: redox signaling and oxidative stress. Journal of Biological Chemistry, 289(13): 8735-8741.
7. Beevi, S. S. S., Rasheed, A. M. H. & Geetha, A. 2004. Evaluation of oxidative stress and nitric oxide levels in patients with oral cavity cancer. Japanese Journal of Clinical Oncology, 34(7): 379-385.
8. Lourdhu Mary, A., Nithya, K., Isabel, W. & Angeline, T. 2014. Prevalence Of Catalase (-21 A/T) Gene Variant In South Indian (Tamil) Population. Biomed Research International, 2014.

9. Hadwan, M. H. 2018. Simple spectrophotometric assay for measuring catalase activity in biological tissues. BMC biochemistry, 19(1): 1-8.
10. Goyal, M. M. & Basak, A. 2010. Human catalase: looking for complete identity. Protein & cell, 1(10): 888-897.
11. Ilyukha, V. A. 2001. Superoxide dismutase and catalase in the organs of mammals of different ecogenesis. Journal of Evolutionary Biochemistry and Physiology, 37(3): 241-245.
12. Jeeva, J. S., Sunitha, J., Ananthalakshmi, R., Rajkumari, S., Ramesh, M., & Krishnan, R. 2015. Enzymatic antioxidants and its role in oral diseases. Journal of pharmacy & bioallied sciences, 7(Suppl 2), S331.
13. Goyal, M. M. & Basak, A. 2010. Human catalase: looking for complete identity. Protein & cell, 1(10): 888-897.
14. Carpena, X., Soriano, M., Klotz, M. G., Duckworth, H. W., Donald, L. J., Melik-Adamyan, W. & Loewen, P. C. 2003. Structure of the clade 1 catalase, CatF of Pseudomonas syringae, at 1.8 Å resolution. Proteins: structure, function, and bioinformatics, 50(3): 423-436.
15. Ko, T. P., Safo, M. K., Musayev, F. N., Di Salvo, M. L., Wang, C., Wu, S. H. & Abraham, D. J. 2000. Structure of human erythrocyte catalase. Acta Crystallographica Section D: Biological Crystallography, 56(2): 241-245.
16. Sandamalika, W. G., Kwon, H., Lim, C., Yang, H. & Lee, J. 2021. The possible role of catalase in innate immunity and diminution of cellular oxidative stress: Insights into its molecular characteristics, antioxidant activity, DNA protection, and transcriptional regulation in response to immune stimuli in yellowtail clownfish (Amphiprion clarkii). Fish & Shellfish Immunology, 113: 106-117.
17. Shahid, M. N., Amjad, M., Ashraf, U., Jamal, A. & Wattoo, J. I. 2022. Computational Analysis Of Catalase From Different Source Organisms. Pak. J. Bot, 54(1): 363-369.
18. Riccardi, C. M., Cole, K. S., Benson, K. R., Ward, J. R., Bassett, K. M., Zhang, Y. & Kumar, C. V. 2014. Toward "stable-on-the-table" enzymes: Improving key properties of catalase by covalent conjugation with poly (acrylic acid). Bioconjugate chemistry, 25(8): 1501-1510.
19. Nishikawa, M., Hashida, M., Takakura, Y. 2009. Catalase delivery for inhibiting ROS-mediated tissue injury and tumor metastasis. Adv. Drug Deliv. Rev. 61: 319-326.
20. Okuno, Y., Matsuda, M., Miyata, Y., Fukuhara, A., Komuro, R., Shimabukuro, M., Shimomura, I. 2010. Human catalase gene is regulated by peroxisome proliferator activated receptor-gamma through a response element distinct from that of mouse. Endocr. J. 57: 303-309.
21. Yang, W., Zhang, J., Wang, H., Shen, W., Gao, P., Singh, M., Fang, N. 2011. Peroxisome proliferator-activated receptor γ regulates angiotensin II-induced catalase downregulation in adventitial fibroblasts of rats. FEBS Lett. 585: 761-766.
22. Girnun, G. D., Domann, F. E., Moore, S. A., Robbins, M. E. 2002. Identification of a functional peroxisome proliferator-activated receptor response element in the rat catalase promoter. Mol. Endocrinol. 16: 2793-801.
23. Schulz, E., Gori, T., & Münzel, T. 2011. Oxidative stress and endothelial dysfunction in hypertension. Hypertension Research, 34(6): 665-673.
24. Snezhkina, A. V., Kudryavtseva, A. V., Kardymon, O. L., Savvateeva, M. V., Melnikova, N. V., Krasnov, G. S. & Dmitriev, A. A. 2019. ROS generation and antioxidant defense systems in normal and malignant cells. Oxidative medicine and cellular longevity.
25. Volpe, C. M. O., Villar-Delfino, P. H., Dos Anjos, P. M. F. & Nogueira-Machado, J. A. 2018. Cellular death, reactive oxygen species (ROS) and diabetic complications. Cell death & disease, 9(2): 1-9.
26. Robertson, R. P. 2004. Chronic oxidative stress as a central mechanism for glucose toxicity in pancreatic islet β-cells in diabetes. Journal of Biological Chemistry, 279(41): 42351-42354.
27. Chen, Y. T. 2001. The metabolic and molecular bases of inherited disease. Glycogen storage diseases, 1521-1551.
28. Cade, W. T. 2008. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Physical therapy, 88(11): 1322-1335.
29. Zheng, Y., He, M. & Congdon, N. 2012. The worldwide epidemic of diabetic retinopathy. Indian journal of ophthalmology, 60(5): 428.
30. Haffner, S. M., Fong, D., Stern, M. P., Pugh, J. A., Hazuda, H. P., Patterson, J. K. & Klein, R. 1988. Diabetic retinopathy in Mexican Americans and non-Hispanic whites. Diabetes, 37(7): 878-884.
31. Gimbrone Jr, M. A. & García-Cardeña, G. 2016. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circulation research, 118(4): 620-636.
32. Çimen, M. B. 2008. Free radical metabolism in human erythrocytes. Clinica chimica acta, 390(1-2): 1-11.

33. Quan, F., Korneluk, R. G., Tropak, M. B., Gravel, R. 1986 Isolation and characterization of human catalase gene. Nucleic Acids Res. **14**: 5321-5335.
34. Goth, L. & Nagy, T. 2013. Inherited catalase deficiency: is it benign or a factor in various age related disorders?. Mutation Research/Reviews in Mutation Research, 753(2): 147-154.
35. Kodydková, J., Vávrová, L., Kocík, M. & Zak, A. 2014. Human catalase, its polymorphisms, regulation and changes of its activity in different diseases. Folia biologica, 60(4): 153.
36. Chambliss, J. M., Ansar, M., Kelley, J. P., Spratt, H., Garofalo, R. P. & Casola, A. 2020. A polymorphism in the catalase gene promoter confers protection against severe RSV bronchiolitis. Viruses, 12(1): 57.
37. Kadam, D. A., Kalamkar, S. D., Saraf, A., Pathan, I., Acharya, J., Pekhale, K. and Ashma, R. 2022. SNPs in the catalase promoter: a study based on Indian diabetic individuals. International Journal of Diabetes in Developing Countries, 1-8.
38. Góth, L., Rass, P. & Páy, A. 2004. Catalase enzyme mutations and their association with diseases. Molecular Diagnosis, 8(3): 141-149.
39. Bokhary, K., Aljaser, F., Abudawood, M., Tabassum, H., Bakhsh, A., Alhammad, S. & Alsubki, R. 2021. Role of Oxidative Stress and Severity of Diabetic Retinopathy in Type 1 and Type 2 Diabetes. Ophthalmic Research, 64(4): 613-621.
40. Góth, L. 2006. Reactive oxygen species, hydrogen peroxide, catalase and diabetes mellitus. Redox Report, 11(6): 281-282.
41. Kimoto, K., Suzuki, K., Kizaki, T., Hitomi, Y., Ishida, H., Katsuta, H. & Ohno, H. 2003. Gliclazide protects pancreatic β-cells from damage by hydrogen peroxide. Biochemical and biophysical research communications, 303(1): 112-119.
42. Bokhary, K., Aljaser, F., Abudawood, M., Tabassum, H., Bakhsh, A., Alhammad, S. & Alsubki, R. 2021. Role of Oxidative Stress and Severity of Diabetic Retinopathy in Type 1 and Type 2 Diabetes. Ophthalmic Research, 64(4): 613-621.