Glutathione S-transferases Detoxify Endogenous and Exogenous Toxic Agents- Minireview

Abstract
Glutathione S-transferases (GSTs) are belongs to phase II detoxification enzymes which play an important role in detoxification/biotransformation of endogenous and exogenous toxic agents like reactive oxygen species (ROS), reactive nitrogen species (RNS) and xenobiotic including environmental carcinogens. The generation of reactive oxygen/nitrogen species is known as oxidative stress which causes molecular damage. Oxidation of proteins leads to loss of certain function. Oxidation of lipids causes the disruption of biological membrane. That the DNA mutation and oxidative DNA lesions which are critical in carcinogenesis. This mini review discussed about the detoxification role of GSTs against endogenous and exogenous toxic compounds.

Keywords: Glutathione S-transferases; Endogenous & exogenous toxic agents; Molecular damage

Introduction
The biotransformation of foreign substances (xenobiotic) including drugs in the body is divided into phase I, II and III. But phase II enzymes are playing a key role in the biotransformation of endogenous compounds and xenobiotics to easily excretable forms and also the metabolic inactivation of pharmacologically active substances. The phase II enzymes can perform biotransformation through conjugation reactions. Glutathione S-transferases (GSTs) are one of the versatile detoxification enzymes among phase II enzymes, which are involved in the xenobiotic metabolism and play major role in cellular protection against oxidative stress. GSTs (EC. 2.5.2.18) are belongs to a family of multifunctional enzymes which conjugate electrophilic intermediates with the endogenous tripeptide glutathione (GSH) [1]. GSTs are ubiquitous, multitalented enzymes which catalyse the nucleophilic addition of the glutathione (Glu-Cys-Gly) to numerous hazardous xenobiotic including phase I electrophilic and carcinogenic metabolites [2]. There are cytosolic, mitochondrial and membrane associated GSTs, but detoxification is the key function of cytosolic GSTs [1]. Mammalian cytosolic GSTs are extensively studied [3].

Molecular degeneration
The oxidative stress arises from an imbalance between oxidants and antioxidant enzymatic system. Which causes the oxidation of biomolecules with consequent loss of biological functions of them and it leads to potential oxidative damage to cells and tissues. The accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) shows numerous deleterious effects such as lipid peroxidation; protein oxidation and DNA damage [4].

Disruption of lipids
That the lipid peroxidation occurs in two forms in the biological system, the participation of cyclooxygenase and lipooxygenase in the oxidation of fatty acids known as enzymatic lipid peroxidation, participation of transition metal, the ROS, RNS in the fatty acid oxidation, called as non-enzymatic lipid peroxidation [5]. The lipid peroxidation disrupts the normal structure and function of lipid bilayers of membrane which surrounding both cell and organelles. That the lipid peroxidation which can alter membrane permeability, transportation and fluidity [6].

Oxidation of proteins
Carbonyl derivatives of certain amino acids like proline, lysine, arginine and threonine oxidation are used as markers for oxidative stress. That the oxidation of aromatic amino acids like tyrosine, various products are formed due to interaction either ROS (di-tyrosine) or RNS (3-nitrotyrosine) [7]. That the modified proteins by oxidation are usually recognized and degraded in the cells, but some oxidized proteins are accumulate over time and lead to cellular dysfunction. That the lipofuscin which is a brown-yellow pigment, it is a product of iron-catalysed oxidation (polymerization) of proteins and lipids, which is extremely resistant to proteolysis, it accumulates and which is used as an aging marker [8].

Oxidation of Nucleic acids
Oxidative stress can lead to different lesions in DNA which are direct modification of bases of nucleotides including single and double strands breaks. Among all the bases of the nucleotides, guanine is most susceptible to oxidative changes, due to its lower reduction potential and hydroxyl radicals interact with imidazole ring of this nitrogenous base [9]. The well-studied marker for...
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1. Hayes JD, Flanagan JU, Jowsey IR (2005) Glutathione transferases. Annu Rev Pharmacol Toxicol 45: 51-80.
2. Senhaji N, Kassogue Y, Fahimi M, Serbati N, Badre W, Nafidi S (2015) Genetic polymorphisms of multidrug resistance gene-1 (MDR1/ABCB1) and glutathione S-transferase gene and the risk of inflammatory bowel disease among Moroccan patients. Mediators Inflamm 2015: 248060.
3. Frova C (2006) Glutathione transferases in the genomics era: new insights and perspectives. Biomatol Eng 23(4): 149-169.
4. Lushchak VI (2014) Free radicals, reactive oxygen species, oxidative stress and its classification. Chemico-Biol Interactions 224: 164-175.
5. Ayala A, Muñoz MF, Argüelles S (2014) Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev 2014: 1-31.
6. Morita M, Naito Y, Yoshikawa T, Niki E (2016) Plasma lipid oxidation induced by peroxynitrite, hypochlorite, lipoxygenase and peroxyl radicals and its inhibition by antioxidants as assessed by diphenyl-1-pyrenylphosphine. Redox biology 8: 127-135.
7. Pisoschi AM, Pop A (2015) The role of antioxidants in the chemistry of oxidative stress and its classification. Eur J Med Chem 97: 55-74.
8. Aslanli BA, Ghorab S (2016) Studies on oxidants and antioxidants of oxidative stress: a review. Eur J Med Chem 97: 55-74.

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Oxidation of DNA is 8-hydroxydeoxyguanosine which is a product of guanosine oxidation by HO" [7,10], this product can pair with adenine and generate a GC/TA mutation upon replication [10]. The most relevant marker is the homologue 8-hydroxyguanosine for RNA oxidation. The RNA if more frequently oxidized than DNA, because of its closer localization to ROS and RNS occurrence in cell. That the major consequences of RNA oxidation are the breakage of strand and ribosomal dysfunction, preventing correct protein production [7].

Detoxification of endogenous hazardous agents

Glutathione S-transferases (GSTs) are detoxifying a large number of endogenous toxic agents like carcinogens, drugs and environmental pollutants. The chemotherapeutic agents of cancer such as adriamycin, 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU), busulfan, Carmustine, chlorambucil, cis-platin, crotonoyloxymethylen-2-cyldohexenone (COMC-6), melphalan, mitozantrone, thiopeta, cyclophosphamide and ethacrynic acid are detoxified by GSTs [11]. Environmental chemicals and their metabolites like acrolein, atrazine, DDT, inorganic arsenic, lindane, Malathion, methyl parathion, mucosaldehyde and tridiphane are detoxified by GST isoenzymes [12,13]. A large number of epoxides like fosfomycin and those derived from environmental carcinogens, polyaromatic hydrocarbons (PAHs) are detoxified by GST. Activated metabolites N-acetoxy-PhIP of heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) which produced by cooking protein-rich food is also detoxified by cytosolic GST.

Activation of xenobiotics

The conjugation reaction catalysed by GST can form less reactive and readily excreted products. But in some cases that the glutathione (GSH) conjugate is more reactive than the parent compound like short chain alkyl halides that contain two functional groups and 1, 2-dihaloethanes, where the GSH conjugate rearranges to form an episulfonium intermediate which responsible for DNA modification [14,15]. The conjugation of GSH with the solvent dichloromethane facilitate formation of the highly unstable Schloromethlglutathione which capable to modify DNA [14,15].

That the moderately toxic compounds like allyl-, benzyl-, phenethyl-isothiocyanates and sulfuronate are reversibly conjugated with GSH by GST to form thiocarbanates which spontaneously degrade to their isothiocyanates by releasing GSH. Again that the isothiocyanates may be taken up by the cell and re-conjugated with GSH and then form thiocarbanate and then revert to the isothiocyanate. Due to this cyclic process, intracellular GSH levels are decreased and facilitate the distribution of isothiocyanates entire the body. Such isothiocyanate either low GSH content or not conjugated with GSH, but rather are more likely to thiocarbanate proteins, which result in cell death [16].

Detoxification of endogenous hazardous agents

The GSTs is exhibits moderate role in lipid peroxidation in biological membranes known as non-selenium glutathione peroxidase (GPxs) activity.

The non-selenium (GPxs) shows activity with 1-palmitoyl-2-(13-hydroperoxy-cis-9, trans-11-octadecadienoyl)-L-3-phosphadylcholine, phosphatidylcholinehydroperoxide and reducing lipid hydroperoxides which are in membranes [17-19].

The transferases can reduce cholesterylhydroperoxides [20], fatty acid hydroperoxides, (S)-9-hydroxy-10, 12-octodecadecionic acid and (S)-13-hydroperoxy-9, 11-octodecadecionic acid [21]. That the lipid peroxidation end products like 2-alkenals acrolein, crotonaldedyde and 4-hydroxy-2-alkenals are conjugate with GSH by GSTs [21]. GSTs catalyze the GSH conjugation with cholesterol-5, 6-oxide, epoxycisatrienoic acid and 9, 10-epoxyeicosaenoic acid, which indicating its role in cellular protection against oxidative stress by harmful electrophiles [1].

Conclusion

Both endogenous and exogenous toxic agents are exhibiting numerous deleterious effects on biological system. Theses toxic agents have impact on molecular damage. However, the biological system has been developed an efficient antioxidant enzymatic system. GSTs are multifunctional antioxidant enzymes which have non selenium glutathione (GSH) peroxidase (GPxs) activity in addition to GSH transferase activity. By these two activities, GSTs detoxifying wide range of hazardous substances.

Conflict of Interest

Authors do not have any potential conflict of interest.

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References

1. Hayes JD, Flanagan JU, Jowsey IR (2005) Glutathione transferases. Annu Rev Pharmacol Toxicol 45: 51-80.
2. Senhaji N, Kassogue Y, Fahimi M, Serbati N, Badre W, Nafidi S (2015) Genetic polymorphisms of multidrug resistance gene-1 (MDR1/ABCB1) and glutathione S-transferase gene and the risk of inflammatory bowel disease among Moroccan patients. Mediators Inflamm 2015: 248060.
3. Frova C (2006) Glutathione transferases in the genomics era: new insights and perspectives. Biomatol Eng 23(4): 149-169.
4. Lushchak VI (2014) Free radicals, reactive oxygen species, oxidative stress and its classification. Chemico-Biol Interactions 224: 164-175.
5. Ayala A, Muñoz MF, Argüelles S (2014) Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev 2014: 1-31.
6. Morita M, Naito Y, Yoshikawa T, Niki E (2016) Plasma lipid oxidation induced by peroxynitrite, hypochlorite, lipoxygenase and peroxyl radicals and its inhibition by antioxidants as assessed by diphenyl-1-pyrenylphosphine. Redox biology 8: 127-135.
7. Pisoschi AM, Pop A (2015) The role of antioxidants in the chemistry of oxidative stress: a review. Eur J Med Chem 97: 55-74.
9. Smith JA, Park S, Krause JS, Banik NL (2013) Oxidative stress, DNA damage, and the telomeric complex as therapeutic targets in acute neurodegeneration. Neurochemistry International 62(5): 764-775.

10. De Bont R, Van Larebeke N (2004) Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis 19(3): 169-185.

11. Hamilton DS, Zhang X, Ding Z, Hubatsch I, Mannervik B, et al. (2003) Mechanism of the glutathione transferase-catalyzed conversion of antitumor 2-crotonoyloxymethyl-2-cycloalkenones to GSH adducts. J Am Chem Soc 125(49): 15049-15058.

12. Abel EL, Bammler TK, Eaton DL (2004) Biotransformation of methyl parathion by glutathione S-transferases. Toxicol Sci 79(2): 224-232.

13. Abel EL, Opp SM, Verlinde CL, Bammler TK, Eaton DL (2004) Characterization of atrazine biotransformation by human and murine glutathione S-transferases. Toxicol Sci 80(2): 230-238.

14. Guengerich FP, McCormick WA, Wheeler JB (2003) Analysis of the kinetic mechanism of haloalkane conjugation by mammalian θ-class glutathione transferases. Chem Res Toxicol 16(11): 1493-1499.

15. Wheeler JB, Stourman NV, Thier R, Dommermuth A, Vuilleumier S, et al. (2001) Conjugation of haloalkanes by bacterial and mammalian glutathione transferases: mono- and dihalomethanes. Chem Res Toxicol 14(8): 1118-1127.

16. Xu K, Thornton PJ (2001) Involvement of glutathione metabolism in the cytotoxicity of the phenethylisothiocyanate and its cysteine conjugate to human leukaemia cells in vitro. Biochem Pharmacol 61(2): 165-177.

17. Li J, Xia Z, Ding J (2005) Thioredoxin-like domain of human κ class glutathione transferase reveals sequence homology and structure similarity to the θ class enzyme. Protein Sci 14(9): 2361-2369.

18. Yang Y, Sharma R, Zimniak P, Awasthi YC (2002) Role of α class glutathione S-transferases as antioxidant enzymes in rodent tissues. Toxicol Appl Pharmacol 182(2): 105-115.

19. Prabhu KS, Reddy PV, Jones EC, Liken AD, Reddy CC (2004) Characterization of a class alpha glutenathione-S-transferase with glutathione peroxidase activity in human liver microsomes. Arch Biochem Biophys 424(1): 72-80.

20. Hamdy SI, Hiratsuka M, Narahara K, Endo N, El-Enany M, (2003) Genotype and allele frequencies of TPMT, NAT2, GST, SULT1A1 and MDR-1 in the Egyptian population. Br J Clin Pharmacol 55(6): 560-569.

21. Liang T, Habegger K, Spence IB, Foroud T, Ellison JA, et al. (2004) Glutathione S-transferase B-8 Expression Is Lower in Alcohol-Preferring Than in Alcohol-Nonpreferring Rats. Alcohol Clin Exp Res 28(11): 1622-1628.