

REVIEW ARTICLE

Glutathione S-transferase is a good biomarker in acrylamide induced neurotoxicity and genotoxicity

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ABSTRACT

Glutathione S-transferases (GSTs) are major defence enzymes of the antioxidant enzymatic system. Cytosolic GSTs are more involved in the detoxification than mitochondrial and microsomal GSTs. GSTs are localized in the cerebellum and hippocampus of the rat brain. Acrylamide (AC) is a well assessed neurotoxin of both animals and humans and it produces skeletal muscle weakness and ataxia. AC is extensively used in several industries such as cosmetic, paper, textile, in ore processing, as soil conditioners, flocculants for waste water treatment and it is present in daily consumed food products, like potato chips, French fries, bread, breakfast cereals and beverages like coffee; it is detected on tobacco smoking. GST acts as a biomarker in response to acrylamide. AC can interact with DNA and therefore generate mutations. In rats, low level expression of glutathione S-transferase (GST) decreases both memory and life span. The major aim of this review is to provide better information on the antioxidant role of GST against AC induced neurotoxicity and genotoxicity.

KEY WORDS: glutathione S-transferases; biomarker; acrylamide; neurotoxicity; genotoxicity

Introduction

Glutathione S-transferases (GSTs) (EC 2.5.1.18) are multifunctional phase II versatile detoxification and xenobiotic metabolizing enzymes (Hayes *et al.*, 2005; Frova, 2006). There are seven classes of cytosolic glutathione S-transferases identified in mammals, which are classified on the basis of amino acid sequence similarities, named as alpha (α), mu (μ), pi (π), sigma (σ), theta (θ), omega (ω) and zeta (ξ) (Hayes & McLellan, 1999; Sheehan *et al.*, 2001).

Detoxification role of GST

The cytosolic GST isoenzymes belong to the same class sharing greater than 40% identity. Between different classes the identity is less than 25% (Hayes *et al.*, 2005). GSTs are ubiquitous and inactivation of cancerous agents through metabolism makes them important in cancer therapy (certainly alpha, mu, pi and theta class GSTs

(Lo *et al.*, 2007). The tri-peptide glutathione (GSH) is an efficient scavenger of reactive oxygen species (ROS). GSTs are responsible for detoxification of oxidative stress by products of metabolism (Hayes *et al.*, 2005). Toxic chemicals, oxidation and variation in temperature can regulate the expression of GSTs (Frova, 2006). The conjugation of electrophilic compounds by GST with glutathione detoxifies harmful drugs and environmental chemicals and thus GSTs are toxicologically important enzymes (Arakawa *et al.*, 2013). Figure 1, shows general reaction catalysed by GST. GSTs are playing a key role in cellular detoxification system to protect the cell from reactive oxygen metabolites and they contribute to biotransformation of xenobiotics and carcinogens (Hayes *et al.*, 2005). GST based drugs would be the next generation therapeutics to deal with drug resistance, cancer as well as neurological and neurodegenerative diseases (Kumar *et al.*, 2017).

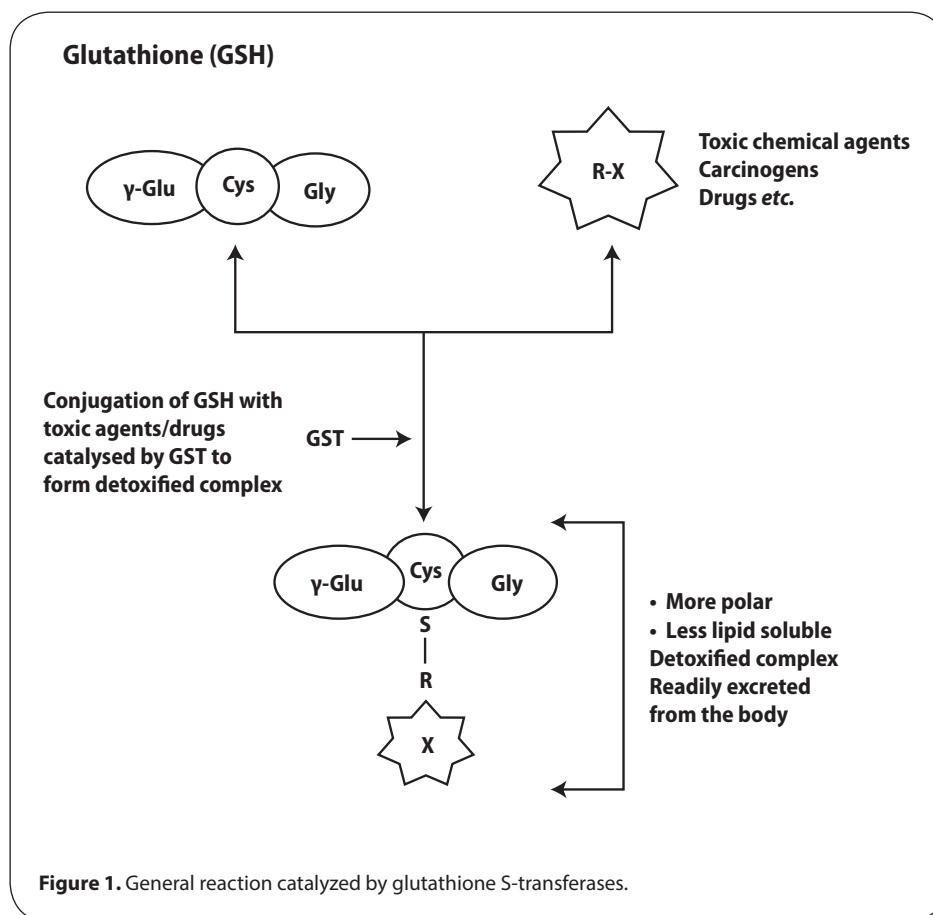
GST enzymes have developed many functions throughout evolution (da Fonesca *et al.*, 2010). The cellular protective role of GST superfamily was taken towards positive selection on GST duplicates and they acquired other functions including sex hormone metabolism and apoptosis regulation which are vital for the retention of duplicates. Metabolism of xenobiotics was the main cause for the expansion of the GST family (da Fonesca *et al.*, 2010).

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GSTs exhibit an adaptive response to cellular stress (Hayes *et al.*, 2005). In addition, cytosolic GST promoter possesses the antioxidant response element (Frova, 2006). Glutathione (GSH) acts as scavenger of reactive oxygen species (ROS) and GSTs are responsible for metabolism of oxidative stress by-products (Hayes *et al.*, 2005). It was identified that soluble GSTs in mitochondria may work against reactive oxygen species (ROS) generated by the respiratory chain (Haider *et al.*, 2002). GST binding to reactive electrophiles may be important for preventing DNA damage. For other molecules GSTs act as intracellular carriers (Hayes *et al.*, 2005). GSTs are multifunctional antioxidant enzymes that exhibit selenium independent glutathione peroxidase (GPx) activity in addition to glutathione transferase (GST) activity. With these activities GST can detoxify a variety of toxic chemicals (Dasari *et al.*, 2017a)

Structural characterization of GST

There are two binding sites in the cytosolic glutathione S-transferases (GSTs), *i.e.* glutathione (GSH) binding site (G site) and substrate (xenobiotic) binding site (H site). Two distinct xenobiotic binding sites are there in rat alpha class GST, including certain GST isoenzymes (Ding *et al.*, 2003).

It is suggested that domain I (G site) is composed of smaller N-terminal α/β helices, which include 1–78 amino acid residues of α and θ class, 1–82 of class μ , 1–74 of class π and σ and domain II (H site) is composed of larger α helix, which includes 86–222 amino acid residues of class α , 90–217 of class μ , 81–207 of class π , 81–202 of class σ and 85–208 of class θ (Armstrong, 1994; Wilce *et al.*, 1995). GST specific activity is decided by amino acid residues in the H-site (Armstrong, 1994).

Brain GSTs

Table 1 shows localization and importance of GST. Several studies reported that alpha (α), mu (μ) and pi (π) class GSTs were purified from rat brain; Yc of α class, Yb and Y β of μ class, Y δ of π class GSTs with relevant molecular weight 27.5 KD, 26.3 KD and 26 KD, and 24.8 KD respectively, are expressed in response to toxic chemicals. Increased levels of total GST activity and relative density of that enzyme was studied in two regions of the brain, *i.e.* cerebellum and hippocampus (Struzynska *et al.*, 2002). The π class GST has been associated with myelin forming cell, probably to protect the myelin structure (Tansey & Cammer, 1991). Several studies reported that Yb and Y β subunits of π class GST are more expressed in the rat brain, which may play a key role in detoxification.

Table 1. Rat brain glutathione S-transferases localization and their role.

Yb3 subunit of μ class GST is specifically expressed in rat brain	Abramovitz & Listowsky, 1987
GST isoenzymes are localized in glial cells of rat brain	Cammer <i>et al.</i> , 1989
π class GST may protect myelin structure	Tansey & Cammer, 1991
GSTA4 of alpha (α) class is localized in ependymal cells of the chorioid plexus, endothelial cells and perivascular endfeet of astrocytes	
Ya subunit in nuclei and Yc subunit in nucleoli of α class GST is localized in rat brain neuron	Johnson <i>et al.</i> , 1993
Both α and μ class GSTs protect neurons from toxic compounds	
GST activity is identified in detectable level in both cerebellum and hippocampus	Struzynska <i>et al.</i> , 2002
GSTA4 and GSTM1 of α and μ class GSTs inhibit oxidative damage to lipids and proteins in rat brain	Shao <i>et al.</i> , 2005
GSTA4 isoenzyme may protect microenvironment of brain cell	Abbott <i>et al.</i> , 2006
Absence of GSTM1 of π class GST is increase the risk of schizophrenia and tardive dyskinesia	De Leon <i>et al.</i> , 2005
Low level expression of GST decrease life span and memory	Bjork <i>et al.</i> , 2006

According to brain immunohistochemical studies, GSTA4 is predominantly distributed in ependymal cells of the chorioid plexus, endothelial cells and perivascular endfeet of astrocytes (Johnson *et al.*, 1993). The GSTA4 isoenzyme in the blood-brain barrier was strategically positioned to defend the microenvironment of brain cells (Abbott *et al.*, 2006). The GSTA4 expression levels were increased and nearly doubled in the cerebral cortex of old rats compared to young adult rats (Martinez-Lara *et al.*, 2003). The absence of GSTM1 increases the risk of schizophrenia and tardive dyskinesia (De Leon *et al.*, 2005). The mood stabilizers, like lithium or valproate, induce expression of both GSTM1 and GSTA4 and they inhibit oxidative damage to lipids and proteins and thus protect the brain from exotoxicity (Shao *et al.*, 2005). A low level of GST expression is associated with a decrease of life span memory performances in rats and it may model assessment of brain aging and neurodegeneration (Bjork *et al.*, 2006).

Immunohistochemical studies reported μ class GST to be localized in astrocytes, subventricular zone cells and ependymal cells (Cammer *et al.*, 1989), π class GST is localized in oligodendrocytes and also in association with myelin (Cammer *et al.*, 1989) of the rat brain central nervous system. Localization of GST Ya subunit was identified in nuclei and Yc subunit in nucleoli of the rat brain neuron (Johnson *et al.*, 1993). There are at least two GST isoenzymes localized in glial cells of the rat brain (Cammer *et al.*, 1989). Yb3 subunit of μ class GST was found to be specifically expressed in the rat brain (Abramovitz & Listowsky, 1987).

Cytosolic GST activity and total concentration of GST protein as well as the concentration of μ class GST are almost equal in the cerebellar cortex of the rat (Johnson *et al.*, 1993). In rats, the cytoplasmic localization of microsomal GST and the nuclear localization of α class GSTs in neurons, the relationship between the concentration of Yb2 subunit of μ class GST and also the resistance of neurons to toxic compounds in the cerebellar cortex indicate that the GSTs may protect against exogenous as well as endogenous neurotoxic metabolites (Johnson *et al.*, 1993).

Role of biomarkers

The environment is continuously loaded by foreign chemicals as well as metals due to urbanization and industrialization. From the beginning of the 20th century several thousands of organic pollutants have been by several ways released into the environment (Helm *et al.*, 2011). Most of these chemicals are undegradable, extremely toxic and accumulated both in territorial and aquatic ecosystems, transported to different environments by air, water and migratory species from their production place (Choi & Wania, 2011). Biochemical markers are useful in examining the effects of toxicants in various tissues (Van der Oost *et al.*, 2003). Figure 2, shows the expression of GST in response to AC. Biochemical markers can provide basic warning signals of particular stress and also give information on the health status of the organism (Korte *et al.*, 2000).

By ecotoxicological studies the interaction between chemicals and the organism can be assessed at different levels by using various biomarkers such as biotransformation enzymes, antioxidative compounds, oxidative

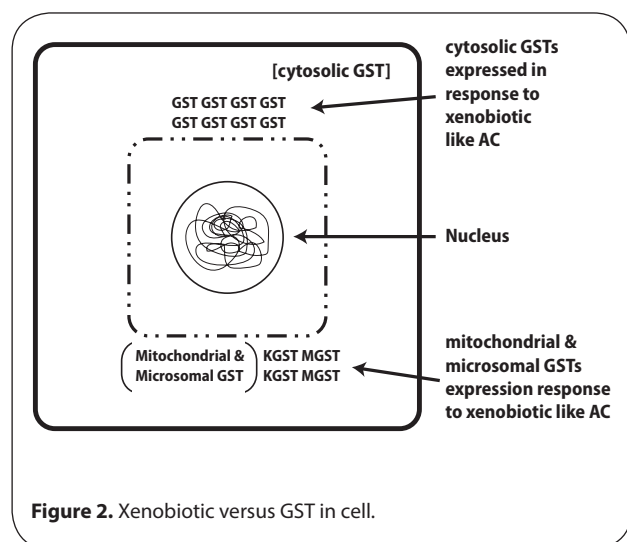


Figure 2. Xenobiotic versus GST in cell.

stress parameters, biotransformation products, stress proteins, both hematological and histological parameters, immunological, reproductive and endocrine parameters, genotoxic, neuromuscular, physiological and morphological and many other parameters (Van der Oost *et al.*, 2003). Most of the xenobiotics are metabolized by conjugation with glutathione (GSH) catalyzed by glutathione-S-transferase (GST) (Zimniak, 2008). A variety of organic xenobiotics, drugs and toxic compounds are metabolized by glutathione S-transferases (Halliwell & Gutteridge, 2015). In response to xenobiotics, the expression of GST as biomarker can be measured with the substrate 1-chloro-2, 4-dinitrobenzene by using spectrophotometer (Habig *et al.*, 1974).

Acrylamide (AC)

Acrylamide (AC) is a very reactive and easily soluble substance in water and it is commonly used in industries as well as laboratories (Nordin *et al.*, 2003). As shown in Figure 3, AC is used in cosmetic, paper and textile industries as well as in ore processing, as soil conditioners and flocculants for waste water treatment (Friedman, 2003). AC is carcinogenic to experimental animals; it was discovered in various food products which are routinely consumed by humans, a situation raised public health concerns (Weiss, 2002). Generally, individuals can be victimized to AC at the work place (Dearfield *et al.*, 1995). AC enters the human diet through carbohydrate and amino acid rich food products prepared at high temperature (during food processing) (Stadler *et al.*, 2002; Mottram *et al.*, 2002); heat treated food products contain AC (Konings *et al.*, 2003). Lower level of AC is formed when cooking at lower temperature (Rydberg *et al.*, 2003). As shown in Figure 3, commonly consumed foods such as breakfast cereals, French fries and potato chips, as well as beverages (e.g., coffee) contain a significant quantity of AC (Tareke *et al.*, 2002).

It is well established that AC once entered into the biological system is quickly passed via cell membranes and widely distributed to all tissues (LoPachin & DeCaprio,

2005). AC shows neurotoxic, mutagenic and carcinogenic effects (Zhang *et al.*, 2011; Maier *et al.*, 2012). AC forms glutathione S-conjugate by interacting with vital cellular nucleophiles having -SH, -NH₂ and -OH groups, which is an initial step of biotransformation of electrophiles to mercapturic acid (Awad *et al.*, 1998). AC interacts with glutathione S-transferases (GSTs) (Das *et al.*, 1982). AC induced oxidative stress is more effective at high doses (Yousef & El-Demerdash, 2006).

Influence of AC on GST

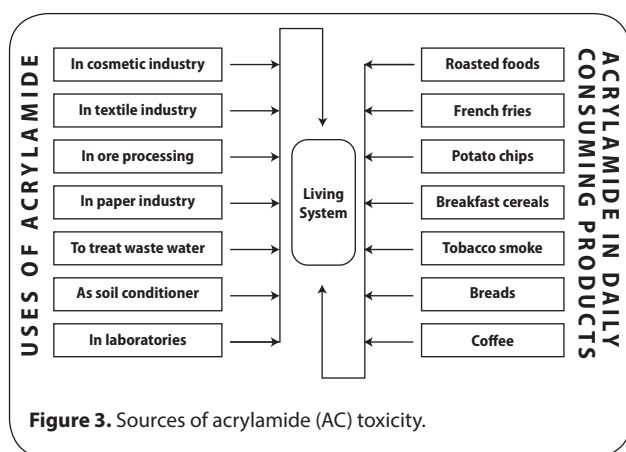
A significant decrease in glutathione (GSH) content and GST activity was observed in AC administered rat brain (Shukla *et al.*, 2002). Depletion of GSH content as well as inhibition of GST activity was found both *in vitro* and *in vivo* (Srivastava *et al.*, 1986). A high level of GST and GST associated peroxidase (GPx) can protect the brain from AC toxicity up to certain level (Dasari *et al.*, 2017b).

Neurotoxicity of AC

The occurrence of adverse changes at the structural and functional level in the nervous system induced by a toxic compound is considered neurotoxicity and the substance responsible for the pathological condition of the nervous system is a neurotoxin (Bull, 2007). AC induced neurotoxic symptoms are characterized as ataxia, skeletal muscle weakness, and cognitive impairment including numbness of the extremities (Deng *et al.*, 1993). AC neurotoxicity in both human and experimental models was associated with cerebellar Purkinje cell death, degeneration of distal axons and nerve terminals in both the peripheral and central nervous systems (PNS and CNS) (LoPachin *et al.*, 2003).

Several rat studies suggest that axon degeneration might not be a primary neurotoxic effect of AC (Lehning *et al.*, 2003). Long-term treatment and low-dose administration of AC lead to degeneration of peripheral nerve tissue such as sciatic, tibial and sural nerves. Silver stain study of rat cerebellum revealed that AC can induce progressive degeneration of Purkinje cell axons (Lehning *et al.*, 2003). Central-peripheral neuropathy was observed in rats, monkeys and humans exposed to AC (Seale *et al.*, 2012). Allam *et al.* (2013) identified AC toxicity in the cerebral cortex as pyknosis and neurocyte chromatolysis in all stages of their investigation.

When the adduct formation exceeds and intoxication continues up to a disproportional increase of dysfunctional proteins, the related presynaptic processes are progressively disabled, which leads to the characteristic cumulative neurotoxicity of AC (LoPachin *et al.*, 2006). AC was found to suppress both metabolism and axonal transport in neurons, which leads to deficiency of nutritional factors (Honing & Rosenberg, 2000). Both prenatal and perinatal exposure of rodent pups to AC causes developmental neurotoxicity (Garey & Paule, 2010). The



accumulation of weak type-2 alkene electrophiles such as AC, methyl acrylate, ethyl methacrylate accelerate the progressive nerve terminal demise associated with Alzheimer's disease (LoPachin & Gavin, 2012). Both cerebellar dysfunctions and proprioceptive sensations are causes for abnormal performances after AC administration (Allam *et al.*, 2011).

Genotoxicity of AC

Toxicogenomic studies are based on gene expression evaluation to detect toxicity signals and identify new sensitive markers (Ellinger-Ziegelbauer *et al.*, 2008). Yet the specificity of thousands of genomic biomarkers are sometimes confuse and thereby not significant enough (Zhang *et al.*, 2011). When gametes are subjected to artificial reactive oxygen species (ROS) DNA damage may occur, such as modification of all bases, generation of base-free sites, deletions, frameshifts, DNA cross links, including chromosomal rearrangements (Duru *et al.*, 2000). Figure 2 shows the expression GST in response to AC.

DNA adduct formation is completely non-dose dependent and mutations can form at lower concentrations of AC, indicating the generation of promutagenic DNA adducts (Besaratina & Pfeifer, 2003). Both AC and glycidamide (GC) (epoxide metabolite of AC) can damage DNA and glycidamide is mainly responsible for the mutagenicity of AC (Besaratina & Pfeifer, 2004). Even micromolar doses of AC can effectively induce promutagenic DNA adducts and this calls for a reconsideration of AC presence in human diet as well as in the environment (Besaratina & Pfeifer, 2004).

Adler *et al.* (1993) suggested that AC can generate chromosomal aberrations, sister chromatid exchanges, and mitotic disturbances. Both chromosomal aberration and micronucleus assays proved that AC might have genotoxic potency (Yang *et al.*, 2005). In AC treated rats, feulgen stain (specific for DNA) color intensity is decreased in the medulla neurons when compared to control, due to a marked loss of DNA in the medulla neurons (Allam *et al.*, 2013). During the process of apoptosis, serious and irreversible DNA damage occurs. Glutathione S-transferases and its peroxidase activities are destabilized by the excess accumulation of AC, leading to interaction with DNA (Sreenivasulu & Balaji, 2016).

Conclusion

This review summarizes the neuro and geno-toxicity of AC and the important role of GSTs in detoxification of toxic chemical agents like AC, and their localization in the brain, *i.e.* the cerebellum, hippocampus, neurons and glial cells. AC is a neurotoxin with symptoms like ataxia, skeletal muscle weakness, cognitive impairment and numbness. AC is a potent genotoxic agent forming chromosomal aberrations and micronuclei. Glutathione conjugation with toxic agents, catalyzed by GSTs, is the

most important phase of detoxification. High expression of GST in cytotoxic conditions reveals that it is an efficient biomarker and enhances more tolerance of biological systems to toxic chemicals.

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