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 (ζ) (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 Fonseca 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 Fonseca 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 Yβ of μ class, Yδ 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 Yβ subunits of π class GST are more expressed in the rat brain, which may play a key role in detoxification.
According to brain immunohistochemical studies, GSTA4 is predominantly distributed in ependymal cells of the choroid 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, of schizophrenia and tardive dyskinesia (De Leon et al., 2005). The mood stabilizers, like lithium or valproate, of schizophrenia and tardive dyskinesia (De Leon et al., 2005). The mood stabilizers, like lithium or valproate, of schizophrenia and tardive dyskinesia (De Leon et al., 2005). The mood stabilizers, like lithium or valproate, of schizophrenia and tardive dyskinesia (De Leon et al., 2005). The mood stabilizers, like lithium or valproate, of schizophrenia and tardive dyskinesia (De Leon et al., 2005). The mood stabilizers, like lithium or valproate, of schizophrenia and tardive dyskinesia (De Leon et al., 2005).

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).

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

| Ya subunit in nuclei and Yc subunit in nucleoli of α class GST is localized in rat brain neuron | Johnson et al., 1993 |
| π class GST may protect myelin structure | Tansey & Cammer, 1991 |
| GSTA4 of α class is localized in ependymal cells of the choroid plexus, endothelial cells and perivascular endfeet of astrocytes | Abramovitz & Listowsky, 1987 |
| Low level expression of GST decrease life span and memory | Bjork et al., 2006 |
| GST activity is identified in detectable level in both cerebellum and hippocampus | Struzynska et al., 2002 |
| Both α and µ class GSTs protect neurons from toxic compounds | Abbott et al., 2006 |
| Absence of of GSTM1 increase the risk of schizophrenia and tardive dyskinesia | De Leon et al., 2005 |
| GSTA4 and GSTTM1 of α and µ class GSTs inhibit oxidative damage to lipids and proteins in rat brain | Shao et al., 2005 |
| GST activity is identified in detectable level in both cerebellum and hippocampus | Struzynska et al., 2002 |

### 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.](image-url)
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 & Gutterdige, 2015). In response to xenobiotics, the expression of GST as biomarker can be measured with the substrate 1-chloro-2,4-dinitrobenzene by a 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 concern (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-transfereases (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 neuroocyte 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 (Honig & Rosenberg, 2000). Both prenatal and perinatal exposure of rodent pups to AC causes developmental neurotoxicity (Garey & Paule, 2010). The

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**Figure 3.** Sources of acrylamide (AC) toxicity.
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 promotion of mutagenic DNA adducts (Besaratinia & Pfeifer, 2003). Both AC and glycidamide (GC) (epoxide metabolite of AC) can damage DNA and glycidamide is mainly responsible for the mutagenicity of AC (Besaratinia & 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 (Besaratinia & 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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