CHAPTER 29

BIOCHEMICAL IMPLICATIONS OF TOXIC INSULTS AND CURRENT REGIMENS FOR DETOXIFICATION

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INTRODUCTION

Brief Overview of Types of Toxic Insults

In routine life, humans and animals are exposed to a number of environmental and household toxicants. These compounds alter the normal biochemical processes such as activate or inhibit the enzymes involved in metabolic processes, production of free radicals thus producing a state of oxidative stress as well as may cause the mutation, cytotoxicity, epigenetic changes and abnormal autophagy. Any of such biochemical implication will lead to toxic manifestations in the living system. There are numerous ways for detoxification of such toxic insults such as antidote administration, chelation therapy, use of nutraceuticals, phytochemicals as well as nanomedicines. We shall highlight the above-mentioned topics with particular reference to the pesticides and heavy metals in this chapter.

Pesticide's term is used generally for agrochemicals identification such as fungicides, bactericides, insecticides, herbicides or rodenticides (Sule et al. 2022). Pesticides may be grouped into diverse chemical classes like organophosphates, carbamates, organofluorines, pyrethroids, triazoles and bipyridyl herbicides (Georgiadis et al. 2018). About 2 million tons of pesticides are being utilized globally per annum (Sharma et al. 2019). The World Health Organization (WHO) has appraised that, in developing countries, every year around 3 million workers undergo severe poisoning from pesticides, of which approximately 18,000 of them ultimately die (Min et al. 2017). The exposure mode to pesticide includes the gastrointestinal, dermal and inhalation one (Yurumez et al. 2007).

Metals have numerous commercial and occupational applications as well as diversity of uses in medicines. There are many examples which can be used in this context like chromium and nickel are used widely for stainless steel production that is primarily important for surgical and prosthetic equipment. Arsenic, on other hand, is administered for acute promyelocytic leukemia. Numerous studies have shown that these metals exposure is linked to carcinogenic and toxic effects on human as well as animals (Valko et al. 2005). Drinking water contamination with high levels of chromium and arsenic has been related with lung, liver and skin cancer hence representing a grave threat in several countries. Ineffective product recycling with high metals concentration and continuously increasing consumption of toxic metals anticipates worsening of such issues in future. That's why explication of molecular and biochemical pathways regarding metal induced carcinogenesis is of great attention regarding upgrading of drug designing for anti-cancer moieties as well as risk assessment (Galanis et al. 2009).

Exposure of Toxic Agents with Biological Systems

Interaction of an organism with toxic agent is dependent on the dose reaching at certain site as well xenobiotic's affinity for that site. In case when xenobiotic has interaction with multiple sites, each site will have its own affinity which is measured as dissociation constant Kd (or Km for enzymatic site). With increase in dose, the xenobiotic interacts with an increasing number of diverse sites, with decreasing affinities. In cell culture, and to a reduced degree in whole animals, it is likely to reach concentrations rarely achieved in environment. Thus, a biological ligand interaction with high xenobiotic concentrations may be a valuable tool for mechanistic studies, it does not essentially depict the toxicity site of that same agent at lower concentrations (Ross 2010).

BIOCHEMICAL IMPLICATIONS OF TOXIC INSULTS

Alterations and/or Inhibition of Enzymatic Activity

Xenobiotic interaction with enzymes at sites other than substrate-binding sites may decrease or increase the activity of enzyme. Enzyme activation, increase in maximum enzyme velocity without increasing enzyme amount, may be instigated by allosteric accumulation of co-factor which may help in carrying substrate to juxtaposition at enzymatic site of action. Removal and chelation of co-factor, in contrast, might inhibit enzyme (Ross 2010). There are several examples which can be narrated in this context.

The primary target of organophosphates is acetylcholinesterase (AChE) which hydrolyzes a chief neurotransmitter, acetylcholine (Sharma et al. 2005). Although

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experimental evidences show little correlation between degree of organophosphate produced AChE inhibition. However, organophosphates may result in numerous human body disorders. The organs which might be affected are muscles, kidneys, liver, hematological, immunological systems etc. (Possamai et al. 2007). The prime clinical signs of acute intoxication by organophosphates are irreversible inhibition of enzymatic activity in blood and nervous system which results in acetylcholine accumulation and activation of nicotinic and muscarinic receptors which consequently result to death (Aygun et al. 2007). The swiftness of ACh accumulation mainly depends upon organophosphate exposure level. Acute toxicity is demonstrated as cholinergic crisis and accompanied with miosis, weakness, excessive secretion by glands and muscle fasciculation (Lukaszewicz-Hussain 2010).

Enzyme activity may be altered by heavy metal exposure. Lead poisoning may lead to anemia by inhibition of two important enzymes i.e. δ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase tangled in heme biosynthesis (Mense and Zhang 2006).

Oxidative Stress

Oxidative stress is imbalance between the free radical production and the defense system of body's antioxidants which may be enzymatic or non-enzymatic. Augmented reactive oxygen species (ROS) production and diminution of organism's antioxidant system may result in induction of oxidative stress. ROS are highly unstable as they have one or greater unpaired electrons. That's why, they damage the molecular function and structure in order to get stability by attacking nearby molecules to get another electron. ROS are products of usual metabolic process as well as in cell signal transduction hence show significant role in pathogenesis (Morgan et al. 2007).

All the biological macromolecules such as nucleic acid, protein and lipids may be attacked by free radicals. Lipids, however, are highly vulnerable. The metabolic pathway of cytochrome P450, mitochondrial respiratory chain and inflammation are the main sources for the endogenous production of ROS. ROS may be formed by numerous exogenous sources like metal ions, radiation and chlorinated compounds (Valko et al. 2006).

In chronic or sub-chronic exposures of organophosphates, oxidative stress is considered as prime toxicity mechanism (Ranjbar et al. 2005). Oxidative stress induced by pesticides is instigated by both reactive nitrogen species (RNS) and reactive oxygen species which are linked to numerous diseases including inflammation, neurodegenerative, cardiovascular diseases and cancer. Both RNS and ROS may activate at least five independent signaling pathways including mitochondrial induced apoptosis (Sule et al. 2022). Reactive species are generated in this process. The organophosphate (OP) alter normal homeostasis of antioxidant resulting in depletion of antioxidant, if the prerequisite of constant antioxidants is not sustained (Vidyasagar et al. 2004). In OP toxicity, another way of ROS generation is oxidative phosphorylation inhibition coupled with consumption of high energy as well as increased glucose and ATP release in order to meet energy requirements of body (Milatovic et al. 2006; Rahimi and Abdollahi 2007).

Oxidative stress diminishes the pool of GSH (Zasadowski et al. 2004). GSH levels may also be decreased owing to its partaking in conjugation reactions or reduced cellular ability for regenerating GSH. Intoxication by OP results in oxidative stress which is demonstrated by alterations in activity and/or levels of anti-oxidant enzymes and non-enzymatic antioxidants in different organs respectively. The studies have also demonstrated oxidative stress as augmented concentration of lipid peroxidation marker, malondialdehyde (MDA) and ROS as well (Akhgari et al. 2003). Organophosphate exposure induces hyperglycemia which lead to enhance non-enzymatic glycation by requisite glucose binding or by-products to protein and form complex compounds i.e. advanced glycation end products (AGEs), ultimately leads to functional and structural alteration of protein. Glycated proteins through AGEs activate specific membrane receptors leading to induction of intracellular oxidative stress. Hyperglycemia, thus, is among one of the mechanisms of oxidative stress due to OP intoxication (Rahimi and Abdollahi 2007). A list of different studies regarding *in vitro* and *in vivo* evidences of oxidative stress induced by different pesticides and effect on markers has been shown in Table 1.

Heavy metals also manifest toxicity by production of ROS. Lead (Pb) has great affinity to the reactive –SH group of GSH and may decrease the level of GSH. The antioxidant function of GPx, SOD, CAT, metalloproteins, regarding free radical detoxification might be affected due to Pb exposure. Lead can persuade oxidative damage in diverse organs via directly affecting on membrane lipid peroxidation and hence reducing antioxidant parameters (Kasperczyk et al. 2005; Balali-Mood et al. 2021).

Cellular Deaths, Mutagenicity and Genotoxicity

Dysregulation of cellular proliferation, epigenetic and genetic changes and abnormal activation of pathways of cellular transduction epitomize the key mechanisms of carcinogenesis induced by metals. Base modifications of nucleotide, crosslinking of DNA proteins as well as single and double strand breaks are common genetic effects. Epigenetic effects are primarily linked with histone and DNA methylation leading to inapt gene silencing which ultimately cause alteration in gene expression and tumor development (Salnikow and Zhitkovich 2008; Akhtar et al. 2021). Dysregulation of cellular differentiation and growth is typical feature of cancer phenotype. Various transcription factors, which control prime cellular responses like cell cycle progression and cellular apoptosis, are activated due to dysregulation of cellular proliferation by metals. These transcription factors include tumor suppressor protein p53, AP-1, NFAT and nuclear factors NF-κB (Leonard et al. 2004). Metals, thus, interfere with signal transduction pathways and hence modulate gene expression. The classical PI3K/Akt/mTOR cascade and MAP kinase pathways are targets of various metals.

The main regulator for cellular adaptation to hypoxia is hypoxia inducible factor-1 (HIF-1) (Ke and Costa 2006). It controls many processes perilous for cellular survival like angiogenesis, erythropoiesis, apoptosis, pH regulation and iron metabolism. Raised HIF-1 expression, transcriptional activation and stabilization are related to different cancers like ovarian, lung, prostate, breast cancer etc. (Galanis et al. 2008). HIF-1 is the main integrator of cell signaling pathways which induce tumor angiogenesis. HIF-1, in response to hypoxia activates the vascular endothelial growth factor (VEGF). VEGF scores angiogenesis and tumor progression. Thus, HIF-1 pathway induction is essential for carcinogenesis. Metals can hinder the regulation of HIF-1 by intermingling with HIF-1 hydroxylases or

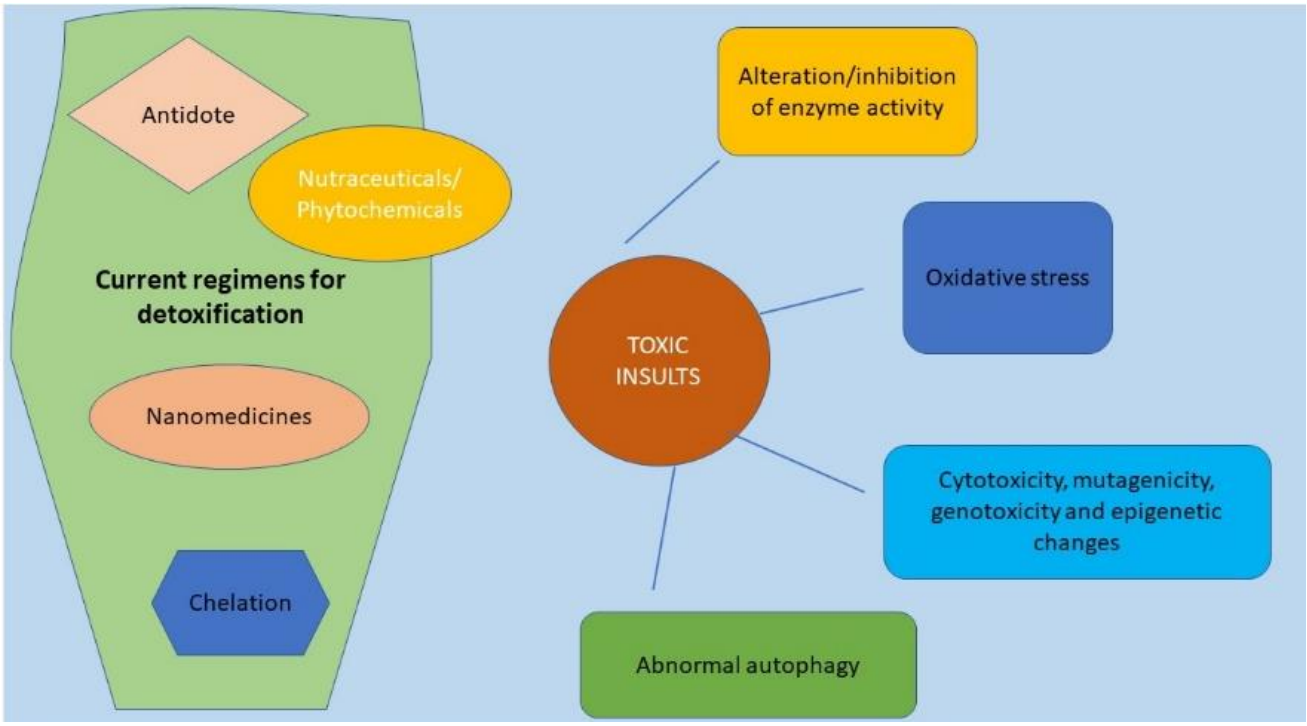

Fig. 1: Schematic diagram showing the possible biochemical implications following toxic insult and current regimens used for detoxification.

Table 1: *In vitro* and *in vivo* evidences regarding involvement of oxidative stress induced by different pesticides

Pesticide name	Mode of study*in vitro*/*in vivo*)	Underlying mechanism	Reference
Chlorfenvinphos	*In vivo* (rats)	Enhancement of lipid peroxidation,	(Lukaszewicz-Hussain 2001)
Diazinon (acute intoxication)		Lipid peroxidation enhancement, altered GPx activity in liver	(Teimouri et al. 2006)
Fenthion	Mice, rats	decreased GSH level and increased MDA in RBCs	(Buyukokuroglu et al. 2008)
Dichlorphos	Fish	Increased GSH, decreased MDA	(Varga and Matkovics 1997)
Quinalphos	Rats	Increase activity of GPx, SOD, GR and CAT in the liver. While GSH and lipid peroxides remained unchanged	(Dwivedi et al. 1998)
Profenofos, λ cyhalothrin, azadirachtin	*Tubifex tubifex*	Initial induction and then reduction in GST and GPx, Throughout induction in CAT and MDA	(Chatterjee et al. 2021)
Cypermethrin	*Oncorhynchus mykiss*	SOD, CAT, GPx activities were increased	(Atamanalp et al. 2021)

Table 2: An insight to heavy metal induced epigenetic changes and carcinogenesis

Name of heavy metal	Carcinogenic class by International Agency for Research on Cancer (IARC)	Underlying mechanisms of cancinogenesis	Reference
Nickel	Possible carcinogen to humans (Group 2B)	Epigenetic alterations, ROS generation and hypoxia signaling pathway activation, disruption of cellular iron homeostasis DNA hypermethylation, alterations of histones modifications, increased heterochromatin condensation	(Ke et al. 2006; Salnikow and Zhitkovich 2008; Zhao et al. 2009)
Vanadium pentoxide	Possible carcinogen to humans (Group-2B)	Vanadate-induced oxidative stress caused expression of HIF-1α and VEGF in human prostate carcinoma cells	(Livage 1991; Gao et al. 2002)
Cobalt	At high doses possible carcinogen (Group-2B)	Inhibition of DNA repair mechanisms, induction of damage of DNA, Aneuploidy and DNA exchange b/w sister-chromatids	(Cancer 1991; Valko et al. 2005)
Arsenic	Carcinogenic to humans (Group1)	Greater cellular proliferation, ROS generation affecting the hypoxia signaling pathway	(Cancer 1987; Simeonova et al. 2000; Huang et al. 2004; Shi et al. 2004)
Chromium	carcinogenic to humans (Group1)	Oxidative stress leading to Cr-DNA adducts, DNA-protein cross-links formation, single and double stranded DNA breaks	(Cancer 1990; Salnikow and Zhitkovich 2008)

by induction of ROS generation which may also activate HIF-1. The underlying carcinogenic mechanism of different metals has been given in Table 2.

Autophagy

An essential catabolic process, mammalian autophagy, involves the degradation of lysosomes and recycling of organelles and cellular proteins. Autophagy is upregulated in metabolic stress conditions such as deprivation of nutrients and greater availability of metabolic intermediate products (Chavez-Dominguez et al. 2020; Saran et al. 2021). Autophagy has shown to escort programmed cell death type II as considered by large intracellular vesicles and the assignation of the autophagy machinery. However, its function, as an active cellular death mechanism remnant controversial (Green and Llambi 2015). Autophagy is introduced by phagophore formation which slowly closes to produce autophagosome, a

double membrane vesicle. Later, it fuses with lysosome to produce autolysosome which permits its contents to be recycled and degraded. Conditions of cellular stress like hypoxia, oxidative stress and ER stress trigger autophagy in order to enable cells for adopting unfavorable conditions (Saran et al. 2021). Endoplasmic reticulum, in mammalian cell, is prime compartment which enables folding of newly synthesized proteins and initiation of vesicle movement. A potent stimulus of autophagy is unfolded protein response (UPR) which is a major ER stress pathway. ER stress sponsors autophagic responses in variety of ways such as UPR downstream effectors RNA-dependent protein kinase-like ER kinase (PERK), induction of Ca+2 and the inositol-requiring protein-1α (IRE1α) pathways (Song et al. 2018). Autophagy is induced by released calcium from ER via activation of the CaMKKβ-AMPK pathways (Borodkina et al. 2016). Carcinogenic metals have been shown to be strong inducers of autophagy. Cancer cells, moreover, take advantage of the autophagic progression to endure aggressive environments. It has been established that heavy metals like Cd and As impair autophagy and hence promote tumorigenesis (Pal et al. 2017), while the successive inhibition of autophagy blocked metal-induced carcinogenesis.

CURRENT REGIMENS FOR DETOXIFICATION

There are various regimens for detoxification. We have discussed few of the currently used such as antidote therapy, chelation therapy, nutraceuticals and medicinal plants for amelioration of toxic insults as well as nanomedicine based novel regimens in this context. A schematic diagram has shown the various biochemical implications and current regimens for detoxification (Figure 1)

Antidotes for Detoxification

Antidotes alter the toxic substance kinetics or change its effect at receptor binding site (Garbino et al. 1997). Antidotes have 4 mechanisms:

A) By neutralizing the effects: OP toxicity is managed with antidotal treatments which consist of two regimens. In pre-treatment, pyridostigmine bromide (acetylcolinestrase inhibitor) is used while in post-treatment, atropine sulphate (anticholinergic) and 2PAM-chloride are used (Gray 1984).

B) By direct action on the involved toxin: Specific binding which is obtained by the chelation, bio-scavenger and immunotherapy for heavy metal, organophosphorus and digoxin respectively (Peter et al. 2007; Pichamuthu et al. 2010). Non-specific binding is obtained by the use of intra-lipid and activated charcoal therapy. The activated charcoal therapy is mostly used for the decontamination of the gastrointestinal toxicity (Merigian and Blaho 2002; Chyka et al. 2005). Salicylate is acidic in nature and it is eliminated by the help of urinary alkalization (Weinberg et al. 1998; Proudfoot et al. 2004; Eddleston et al. 2008; Pillay 2008). C) By decreasing the level of toxic metabolites: Toxic metabolites decrease with the help of binding and convert it to less toxic metabolites.

D) Antidotes acting on the toxin binding site: It can be accomplished by competitive receptor and enzymes inhibition, on the GABA receptor complex e.g. fomepizole and ethyle alcohol are competitive antagonist of ethylene glycol toxicity (Barceloux et al. 2002) and the naloxone is the competitive antagonist for the opioid toxicity by displacing the opioid compound from opioid receptor (Lavonas et al. 2015; Lynn and Galinkin 2018).

Chelation Therapy for Detoxification

Ideal chelator must have low toxicity, same distribution properties just like the heavy metals, highly water soluble, make rapid elimination of toxic substances and have great ability to penetrate the cell membrane (Flora and Pachauri 2010). Different chelators are used for the detoxification of the lead toxicity which bind to the toxin in blood and make them inactive. Edetate Calcium Disodium is given intravenously while succimer/Unithiol is used as oral chelator for the detoxification of lead toxicity (Lowry 2010). Combine therapy is used to attain the synergistic effect of two chelating agents. The combine therapy of DMSA and CaNa2EDTA against the lead poisoning increases the elimination of lead and make a faster recovery (Mishra et al. 2008).

Nutraceuticals and Phytochemicals for Detoxification

Nutraceuticals and phytochemicals which are rich in antioxidants are used for detoxification and amelioration of organ function following toxic insults. Literature has provided many examples in this context.

Quercetin, a flavonoid (Mao et al. 2018) is present in high concentration in onions, soybean potatoes and many fruits, has potential to reduce the oxidation stress and the toxicity which is produced by the cadmium (Wang et al. 2020). Proanthocyanidins, a flavanol, is obtained from the grape seeds and also used for cadmium toxicity (Hemingway and Karchesy 2012). Glufimet, a derivative of glutamic acid, is obtained from the eggs and protein-based food and has ability to detoxify the alcohol insult (Perfilova et al. 2021). P-coumaric acid, an isomer of the coumaric acid, is abundantly present in the fruits and vegetables and has antioxidant activity (Zang et al. 2000; Kong et al. 2013; Pragasam et al. 2013). Naringenin, another flavonoid, present in citrus fruits, grape fruits and tomatoes, has antioxidant property (Pietta 2000). Naringenin decreased the toxic effect of arsenic induce hepato- toxicity in the rat (Mershiba et al. 2013). A carotenoid pigmentlike lycopene, present in excessive amount in the red grape fruit, tomato and watermelon, has ability to reduce the atrazine (herbicide) induced hepatotoxicity (Xia et al. 2016). Turmeric is routinely used nutraceutical and is used to remove heavy metals from the body (Rafati-Rahimzadeh et al. 2014).

In the animal study, the corriander seeds extract also detoxifies the lead toxicity in rat (Sharma et al. 2010). *Terminalia arjuna*, a medicinal herb, has antioxidant activity (Nammi et al. 2003). This medicinal plant also produces cardio protection effect in rat against arsenic toxicity (Manna et al. 2008). *Chenopodium album*, an important medicinal plant, detoxifies the CCL4 induced toxicity (Baldi and Choudhary 2013). *Casuarina equisetifolia* was used against the gentamicin induced nephrotoxicity in the rat and it was found to reduce the toxicity of gentamicin (El-Tantawy et al. 2013).

Calendula officinalis flowers have the neuro-protective property which is evaluated by the monosodium glutamate induced neuro-toxicity in rat. Rats treated with this plant produced less sign of the toxicity induced by monosodium glutamate (Shivasharan et al. 2013). Alpinia galangal has potential to reduce the toxic effect of the anti-cancerous drug like cyclophosphamide (Qureshi et al. 1994).

Few heavy metals like nickel and chromium produces the lipid alteration which is detoxified by the administration of the *Allium sativum* (Gupta et al. 2008). It also contains the potential to reduce the lead induced toxicity in goat, rat and chicken (Hanafy et al. 1994; Senapati et al. 2001; Badiei et al. 2006).

Nanomedicine for Detoxification

Nanomedicine is an emerging field for drug delivery (Akhtar et al. 2020; Akhtar et al. 2020), diagnosis and detoxification now-a-days. Developments in nanotechnology may offer new ways in intoxication support by using nanostructured biomaterials, such as nanoparticles, liposomes, liquid crystalline nano-assemblies, micellar nanocarriers and ligand-based NPs (Muhammad et al. 2017).

Curcumin loaded chitosan nanoparticles are used to detoxify the effect of arsenic toxicity (Yadav et al. 2012). Nanoparticles interact with ozone have great potential to reduce the Aflatoxin B1 produced toxicity (Puzyr et al. 2010). The quercetin, when it is encapsulated in the chitosan/alginate nanoparticles, resulted in increased antioxidant potential (Tzankova et al. 2017). Similarly, curcumin loaded chitosan nanoparticles also improved the oxidative stress status of experimental animals following cypermethrin induced toxicity (Anwar et al. 2020). Cerium oxide (CeO2) nanoparticles have great ability to scavenge the free radical (Rzigalinski et al. 2003; Chen et al. 2006). Another current regimen is use of biomimetic nanosponge for detoxification of toxic substances. These nanosponges are made up of polymeric nanoparticles and coated with biomimetic membranes (Hu et al. 2011).

Conclusion

There are many environmental and household toxic insults which alter the routine biochemical processes. There are many underlying biochemical mechanisms of these toxic reactions. Numerous detoxification strategies are used currently including antidote, chelation therapy, phytochemicals, nutraceuticals and nanomedicines. However, much more working is required in order to have better control on toxic insults.

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