Pesticide Biochemistry and Physiology 112 (2014) 1–6

Contents lists available at ScienceDirect

Pesticide Biochemistry and Physiology

journal homepage: www.elsevier.com/locate/pest

Review

Current view of zinc as a hepatoprotective agent in conditions of chlorpyrifos induced toxicity

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ARTICLE INFO

Article history:
Received 10 October 2013
Accepted 21 April 2014
Available online 6 May 2014

Keywords:
Zinc
Hepatoprotection
Pesticide toxicity

ABSTRACT

Human population bears the brunt of deadly hepatotoxic, neurodegenerative, behavioural and various other developmental disorders due to pesticide toxicity through environmental or occupational exposures. The application of pesticides to control pests in land and water has posed potential health hazards to live stock and wildlife including fishes, mammals, birds and humans. Therefore, various scientific approaches are being considered to tackle the problem of pesticide poisoning especially in developing economies. The role of essential trace elements as the promising and efficient preventive prophylactic agents without any toxicity and side effects in attenuating the adverse effects caused by pesticides, have been reported by various scientists, the world over. In this perspective, zinc, a key constituent of more than 300 mammalian enzymes and many transcription factors has proved its protective potential in various models of animal toxicity. The hepato-protective potential of zinc has been proved during various toxic states including pesticide toxicity. However, zinc warrants further examination with regard to documentation of specific molecular pathways to establish the exact mechanisms for zinc-mediated protection during pesticide toxicity.

Contents

1. Chlorpyrifos toxicity

Amongst many xenobiotics, pesticides on account of their high toxicity and selectivity cause a great concern to human health. Being wide spread environmental contaminants; the anticholinesterase [antiChE] inhibitors compounds are probably the most man-made toxic chemicals. Human population at large is getting constantly exposed to pesticides through food stuffs and drinking water as the pesticides are used to enhance food production in agriculture sector. These compounds get absorbed rapidly by almost all the routes viz. dermal, respiratory, gastrointestinal, are highly lipid soluble and are classified as direct or indirect acetylcholinesterase inhibitors. Pesticides are metabolized primarily by hepatic cytochrome p450 enzymes which further activate indirect

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http://dx.doi.org/10.1016/j.pestbp.2014.04.007
0048-3575/

Table 1
Chlorpyrifos toxicity studies.

Sr. No.	Lead author and year	Chlorpyrifos toxic effect	Molecule/organ/system affected
1	Akhtar et al. (2009) [16]; Ajiboye et al. (2010) [60]; Ouyang et al. (2010) [61]	Inhibition of antichloinesterase	Brain, liver, kidney, spleen
2	Goel et al. (2007) [11]	Cytochrome p450 (drug metablozing enzyme activity)	Liver
3	Goel et al. (2006) [14]	Haematological indices changes, histoarchitecture of RBCs	Blood
4	Goel et al. (2006) [12]	Alterations in carbohydrate metabolizing enzymes	Liver
5	Goel et al. (2005) [78]	Changes in activities of antioxidant defence system enzymes, Hepatic histoarchitecture	Liver, blood
6	Malhotra et al. (2011) [15]	Neurotoxic effects, Behaviour changes	Brain
7	Dow et al. (2002) [3]	Changes in body weight	Liver
8	Wellman and Kramer (2004) [5]	Diarrhoea due to chlolinergic over stimulation	Gastrointestinal system
9	Long et al. (1986) [4]	Breathing problems due to morphological changes in lungs	Respiratory system
10	Cui et al. (2006) [6]	Generation of reactive oxygen species	DNA
11	Tian and Yamauchi (2003) [7]; Tian et al. (2007) [10]	Micronucleus formation	DNA
12	Yano et al. (2000) [8]; Lee et al. (2007) [9]	Carcinogenesis	Lung, brain, liver, stomach

forms of organic phosphorous compounds [1,57,58]. It has been shown that repeated doses of chlorpyrifos were able to cause significant hepatic atrophy [2]. A number of studies have shown that exposure of pesticides in rats caused a significant inhibition of AChE activity in different tissues viz., liver, kidney and spleen [2,59–61]. Also, pesticide exposure generates oxidative stress in the body, as evidenced by increase in thiobarbituric acid reactive substances [TBARS], decrease in the levels of superoxide scavenging enzymes viz., superoxide dismutase [SOD], catalase [CAT] and glutathione peroxidase [GPx] in liver, kidney and spleen[3,62].

Pesticides have been reported to cause ill effects at almost all physiological levels/systems of the mammalian system. Chlorpyrifos resulted in decrease in the body weights of animal subjects upon different time exposures [3]. In respiratory systems, scientific reports have confirmed morphological changes in lungs leading to deaths of rats exposed to chlorpyrifos [4]. Gastrointestinal effects of chlropyrifos caused diarrhoea due to chlolinergic over stimulation [5]. Recent studies on chlorpyrifos demonstrated direct damage to DNA due to induction of reactive oxygen species [6]. Tian and Yamauchi observed micronucleus in 3-day mouse blastocysts following chlorpyrifos maternal exposure [7]. Some studies also addressed the potential carcinogenicity of chlorpyrifos [8,9]. Further, Tian et al. observed the similar results with confirming mitotic catastrophe upon chlorpyrifos exposure [10].

Earlier studies from our laboratory are in sync with above reports as we also observed toxic effects of chlorpyrifos on antioxidant defence enzymes, carbohydrate metabolizing enzymes, drug metabolizing enzymes and histoarchitecture in liver [11–13]. Chlorpyrifos significantly altered ultra-histoarchitecture of red blood cells along with changes in haematological indices [14]. A recent report from our lab also confirmed neurotoxic effects of chlorpyrifos in rat brain [15]. So, the above literature (Table 1) shows wide extent of toxicity caused by chlorpyrifos exposure. However, the present review shall mainly focus on the hepatic toxic effects of chlorpyrifos.

2. Zinc – an overview

Zinc is an essential trace element and is required by all the living organisms because of its critical roles both as a structural component of proteins and as a cofactor in various enzymes mediated biochemical reactions [16]. The importance of zinc in human metabolism is illustrated by the deficiency of zinc which manifests itself in the form of effects which include a diminished immune response, reduced healing, hepatotoxicity and neurological disorders. Zinc has inimitable and broad role in physiological processes. Many biochemical roles of zinc have been reported since the discovery of this element as an essential nutrient for living organisms [17,18] which include roles in enzyme functions [19], nucleic acid metabolism [20,21], cell signaling [22] and apoptosis [23]. Further, the importance of zinc has been investigated in the physiological processes which include growth and development [24,25], lipid metabolism [26], brain and immune functions [27].

On the other hand, deficiency of zinc results in various pathological states. Basically, dietary factors are broadly responsible for zinc deficiency in addition to hereditary factors. However, the symptoms produced during zinc deficiency by either ways are almost similar. The initial effects of zinc deficiency include dermatitis, diarrhea, alopecia and loss of appetite [28,29]. More prolonged deficiency results in growth impairment and neuropsychological changes such as emotional instability, irritability and depression [30,31]. Many studies have reported that zinc deficiency causes decreased immune response which results in increased susceptibility to infections and that may lead to the death of patients [32–34].

The present review provides information on the protection afforded by zinc during hepatotoxicity created by chlorpyrifos pesticides and the molecular mechanisms involved to achieve such mitigating effects.

3. Zinc as an antioxidant

An antioxidant can be defined as any substance that hinders a free radical reaction which involves oxygen. A free radical is any specie that contains one or more unpaired electrons. The antioxidant properties of zinc have been clearly demonstrated in various biochemical systems under different conditions of oxidative stress. The antioxidant mechanism of action of zinc can be broadly divided into two classifications namely chronic effects and acute effects. Chronic effects involve long term exposures of zinc to the subject under investigation which in turn results in the induction of some other substance to be an ultimate antioxidant. The induction of metallothionenis have been reported following chronic exposure to zinc. Metallothioneins are a group of low-molecular-weight [6000–7000 kDa] metal-binding proteins containing 60–68 amino acid residues, of which 25–30% are cysteine. They have the ability to bind 5–7 g zinc [mol/protein] [34–36]. Further, the chronic administration of zinc induces metallothionein under varied toxic states in different organs including brain [37,38], blood [39,40], intestine [41] and liver [42,43].

The second broad classification is acute effects of zinc treatment which further involves two sub-classifications namely protection of sulfhydryl groups and antagonism of the redox active transition metals. The first sub-classification is the mechanism which