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Review article

Permethrin-induced oxidative stress and toxicity and metabolism. A review

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ABSTRACT

Permethrin (PER), the most frequently used synthetic Type I pyrethroid insecticide, is widely used in the world because of its high activity as an insecticide and its low mammalian toxicity. It was originally believed that PER exhibited low toxicity on untargeted animals. However, as its use became more extensive worldwide, increasing evidence suggested that PER might have a variety of toxic effects on animals and humans alike, such as neurotoxicity, immunotoxicity, cardiotoxicity, hepatotoxicity, reproductive, genotoxic, and haematotoxic effects, digestive system toxicity, and cytotoxicity. A growing number of studies indicate that oxidative stress played critical roles in the various toxicities associated with PER. To date, almost no review has addressed the toxicity of PER correlated with oxidative stress. The focus of this article is primarily to summarise advances in the research associated with oxidative stress as a potential mechanism for PER-induced toxicity as well as its metabolism. This review summarises the research conducted over the past decade into the reactive oxygen species (ROS) generation and oxidative stress as a consequence of PER treatments, and ultimately their correlation with the toxicity and the metabolism of PER. The metabolism of PER involves various CYP450 enzymes, alcohol or aldehyde dehydrogenases for oxidation and the carboxylesterases for hydrolysis, through which oxidative stress might occur, and such metabolic factors are also reviewed. The protection of a variety of antioxidants against PER-induced toxicity is also discussed, in order to further understand the role of oxidative stress in PER-induced toxicity. This review will throw new light on the critical roles of oxidative stress in PER-induced toxicity, as well as on the blind spots that still exist in the understanding of PER metabolism, the cellular effects in terms of apoptosis and cell signaling pathways, and finally strategies to help to protect against its oxidative damage.

Abbreviations: 3-PBA, 3-phenoxybenzoic acid; 3-PBAlc, 3-phenoxy-benzylalcohol; 8-OhdG, 8-hydroxy-2′-deoxyguanosine; AchE, acetylcholinesterase; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ANT, anthracene; ARE, antioxidant response element; AUC, area under the tissue concentration-time curve; CA, chromosome aberration; CAT, catalase; CBMN, cytokinesis-block micronucleus; CE, carboxylesterase; CL_{int}, the intrinsic clearance; CoQ_{10}, coenzyme Q_{10}; CY, cypermethrin; CYP, cytochromes P450; Cyt *c*, cytochrome *c*; DCCA, 3-(2,2 dichlorovinyl)-2,2-dimethyl-(1-cyclopropane) carboxylic acid; DEET, *N,N*-diethyl m-toluamide; DNPH, 2,4-dinitrophenylhydrazine; DPPP, diphenyl-1-pyrenylphosphine; Endo III, endonuclease III; ePC, ether PC; Fpg, formamido pyrimidine glycosylase; FTC, fluorescein-5-thiosemicarbazide; GPx, glutathione peroxidase; GSH, glutathione; GSH-R, glutathione reductase; GST, glutathione transferase; GWI, Gulf War Illness; H_2O_2, hydrogen peroxide; hCE, human carboxylesterase; $HO^{\bullet}$, hydroxyl radical; HOO^{-}, perhydroxy radical; iNOS, induced nitric oxide synthase; lyso-PAF, lyso-platelet activating factors; MDA, malondialdehyde; MN, micronucleus; MPO, myeloperoxidase; NO, nitric oxide; Nrf2, Nf-E2 related factor-2; $O_2^{\bullet}-$, superoxide anion; OLE, olive leaf extract; PB, pyridostigmine bromide; PBAld, 3-phenoxybenzylaldehyde; PC, phosphatidylcholine; PCs, protein carbonyls; PER, permethrin; PMNs, polymorphonuclear neutrophils; PND, Post Natal Day; ROS, reactive oxygen species; RNS, reactive nitrogen species; RSV, resveratrol; SCE, sister chromatid exchanges; SOD, superoxide dismutase; t1/2 α, half-life at distribution α phase; t1/2 β, half-life at elimination β phase; Tmax, time needed to reach Cmax (maximum concentration); TA, taurine; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reacting substances; TNF-α, tumour necrosis factor alpha; TNFR, tumour necrosis factor receptor; TOS, total oxidant status; UGT, UDP-glucuronyltransferase

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1. Introduction

The pyrethroid insecticides represent widely used environmental chemicals. Pyrethroids consist of two groups according to their chemical structures: Type I pyrethroids are devoid of a cyano moiety at the α-position (*i.e.* permethrin, PER), while Type II pyrethroids have an α-cyano moiety such as cypermethrin (CY) (Nasuti et al., 2003). According to the symptoms in animals receiving acute toxic doses, Type I pyrethroids cause hyperexcitation, ataxia, tremor and paralysis, while Type II pyrethroids cause hypersensitivity, salivation and choreoathetosis (Ray and Fry, 2006). PER (3-phenoxy-benzyl (±) *cis/trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylate, $C_{21}H_{20}Cl_2O_3$, CAS No. 52645-53-1), the most frequently used synthetic Type I pyrethroid insecticide, is widely used in different forms to control pests in residential areas, the textile industry and agricultural settings, to treat head lice and scabies in humans and fleas in pets, for public health vector control and for disinfection of commercial aircrafts (Anadón et al., 2009, 2013; Bradberry et al., 2005; Nasuti et al., 2003; Navarro et al., 2015; Stout et al., 2009; Turkez and Aydin, 2012; USEPA, 2013; Varloud et al., 2015; Willemin et al., 2015). This extensive use carries the potential for increased human exposure.

Due to the worldwide use of PER, humans and animals may have suffered potential exposure to this compound. The mechanism of PER action is through interference with sodium channels, receptor-ionophore complexes, and neurotransmitters (Imamura et al., 2000). PER is an important insecticide that is used largely because of its two isomeric forms, *cis* and *trans* PER, and due to its high activity as an insecticide and low mammalian toxicity (Nasuti et al., 2008; Rosita et al., 2015). Although it was believed that PER showed low mammalian toxicity, an increasing number of studies have shown that PER can also cause a variety of toxicities in animals and humans, such as neurotoxicity (Carloni et al., 2012, 2013; Falcioni et al., 2010; Gabbianelli et al., 2009b; Nasuti et al., 2014, 2008, 2007b), immunotoxicity (Gabbianelli et al., 2009a; Jin et al., 2010; Olgun and Misra, 2006), cardiotoxicity (Vadhana et al., 2010, 2011a, 2011b, 2013), hepatotoxicity (Gabbianelli et al., 2004, 2013), reproductive (Issam et al., 2011), genotoxic (Turkez and Aydin, 2012, 2013; Turkez and Togar, 2011; Turkez et al., 2012), and haematotoxic (Nasuti et al., 2003) effects, digestive system toxicity (Mahmoud et al., 2012; Sellami et al., 2014b, 2015), anti-androgenic activity (Christen et al., 2014; Xu et al., 2008), fetotoxicity (Erkmen, 2015), and cytotoxicity (Hu et al., 2010) in vertebrates and invertebrates.

Increasing evidence has documented that the toxic effects induced by PER are closely correlated with oxidative stress. PER showed neurotoxic effects that induce oxidative stress in the neonatal rat brain. Prenatal exposure to PER may result in the insufficient development of the brain through alterations of vascular development (Imanishi et al., 2013). PER was documented to have an endocrine disrupting property. It was shown that low doses of PER led to significant disharmony in testosterone concentration along with significant lipoperoxidation in plasma (Issam et al., 2011). PER could induce reproductive toxicity combined with significant oxidative stress. Issam et al. documented that different subcutaneous treatments with low doses of PER resulted in the increased lipid peroxidation, a testis disturbance traduced by a deregulation of spermatogenesis and an epididymis dysfunction by the appearance of strong deformations in the microstructure of the epididymides (Issam et al., 2011). More importantly, PER treatment in early life may have long-term effects changing homeostatic processes, physiological parameters and oxidative stress status in adulthood. Low doses of PER insecticide has long-term consequences leading to cardiac hypotrophy, liver and brain damage, low Ca^{2+} concentrations in leukocytes and plasma, increased Ca^{2+} in the brain and alterations of oxidative stress-related genes, such as Nurr1, NF-κB, Nf-E2 related factor-2 (Nrf2) gene expression levels in old age (Carloni et al., 2012, 2013; Vadhana et al., 2013; Fedeli et al., 2012, 2013; Gabbianelli et al., 2013; Vadhana et al., 2011b). PER also showed toxic effects on sea animals experiencing oxidative stress, such as clams and *Hexaplex trunculus*. It was revealed that PER inhibited AchE activity, resulting in a phase transition in shell composition from aragonite to calcite, and significantly increased oxidative stress (Sellami et al., 2014a, 2015). In addition, PER also induced toxic effects in *Hexaplex trunculus* along with significantly increased antioxidant enzyme levels, such as catalase (CAT) (Mahmoud et al., 2012).

During the toxic mechanism of PER, more than 10 years of studies have suggested that oxidative stress, reactive oxygen species (ROS) and reactive nitrogen species (RNS) may play critical roles in the induction of PER-induced damage to lipids, DNA and proteins in vertebrates and invertebrates. Thus, the influence of oxidative stress, ROS and RNS on PER associated neurotoxicity, immunotoxicity, cardiotoxicity, hepatotoxicity, reproductive, genotoxic and haematotoxic effects, digestive system toxicity, and cytotoxicity has caused increasing attention. To date, several reviews on PER have been published including those that have focused on the following: enantioselective environmental toxicology of chiral pesticides (Ye et al., 2015), human metabolic interactions of environmental chemicals (Hodgson and Rose, 2007), pyrethroid resistance in mosquitoes (Panahi et al., 2015), interactions between multiple insecticide resistance (Hardstone and Scott, 2010), historical tests of the toxicity of pesticides to *Typhlodromus pyri* and their relevance to current pest management (Wearing, 2014), mechanisms of pyrethroid resistance (Kasai et al., 2014), zebrafish as a model system to study toxicology (Dai et al., 2014), insecticide-treated clothes for the control of vector-borne diseases (Baltazar et al., 2014), pesticide exposure as aetiological factors of Parkinson's disease and other neurodegenerative diseases (Baltazar et al., 2014), and so on. In recent years, based on the increasing attention of oxidative stress and toxicities on non-target organisms, a few articles about the important role of oxidative stress in the toxicities of PER have been published. Therefore, it is prudent at this point to review the recent progress into research focused on the toxic mechanism of PER. The scope of this review is primarily intended to summarise the evidence associated with PER-induced toxicity and oxidative stress. The studies related to toxicity of PER and oxidative stress, under both *in vivo* and *in vitro* conditions, are summarised in Tables 1 and 2, respectively. Furthermore, the metabolic pathways, metabolising enzymes, influential factors in the metabolism of PER, and the toxicity of the metabolites of PER are also reviewed. In the future, as the most frequently used type I pyrethroid insecticide, PER presents a great threat to more than just insects, and its toxicity to vertebrates and invertebrates should be carefully investigated. This review summarises the evidence of oxidative stress, ROS or RNS generation, and alterations of antioxidase related to the various types of toxicity caused by PER over the past 10 years. Furthermore, information on the metabolism of PER and various antagonists were also summarised for the application of antioxidants to inhibit PER-induced toxicity.

2. Oxidative stress and toxicity

2.1. Generation of oxidative stress and ROS

Inadequate antioxidant defence or overproduction of free radicals could lead to oxidative stress, which might be initiated by ROS such as hydroxyl radicals ($HO^{\bullet}$), superoxide anions ($O_2^{\bullet -}$), and perhydroxy radicals (HOO^-), and by RNS, including nitric oxide (NO) (Adams et al., 2015; Dasuri et al., 2013; Swomley and