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Science of the Total Environment

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

Hepatotoxicity of paraquat on common carp (*Cyprinus carpio* L.)

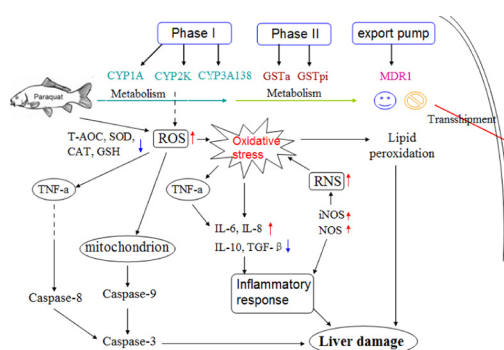
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HIGHLIGHTS

- Paraquat-exposure disturbs the metabolic destabilization of carp liver.
- Paraquat has hepatotoxicity on common carp.
- ROS and RNS may play an important role in paraquat-induced inflammatory response.
- Apoptosis is probably involved in paraquat hepatotoxicity in carp.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 17 August 2017

Received in revised form 22 October 2017

Accepted 22 October 2017

Available online xxxx

Editor: Henner Hollert

Keywords:

Paraquat

Common carp

Hepatotoxicity

Oxidative stress

Inflammatory response

Apoptosis

ABSTRACT

Paraquat (PQ) is a nonselective herbicide that is used worldwide and has been demonstrated to be a high risk to aquatic organisms. However, relatively little is known about the mechanisms on detoxification and hepatotoxicity of PQ in fish. In the present study, a sub-acute toxicity test of PQ exposure on common carp at 1.596 and 3.192 mg L⁻¹ for 7 d was conducted under laboratory conditions. The results showed that the transcriptional levels of cytochrome P450s (CYPs), such as CYP1A, CYP2K, and CYP3A138, GSTα and GSTπ, and export pump gene MDR1, as well as the erythromycin-N-demethylase (ERND) activity were generally up-regulated by PQ exposure for 7 d, indicating that these genes or enzymes are potentially involved in the detoxification of PQ in the fish liver. Further research showed that PQ exposure significantly increased the levels of HSP70, HSP90, NOS, and MDA; promoted expression of pro-inflammatory cytokines, including IL-6 and IL-8; altered the levels of anti-inflammatory cytokines IL-10 and TGF-β, and generally reduced the levels of T-AOC, SOD, CAT, and GSH. In addition, we also found that caspase-3, caspase-8, and caspase-9 were significantly activated in the fish liver following PQ exposure. In brief, the present study showed that PQ exposure induced fish liver injury by destabilizing the metabolism of fish, inhibiting antioxidant enzyme activity, elevating lipid peroxidation, and promoting an immune inflammatory response and apoptosis. The present study further enriches and perfects the mechanism theory of PQ hepatotoxicity to fish, which may be valuable for the risk assessment of PQ and human health protection.

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1. Introduction

Paraquat (PQ) (1-1'-dimethyl-4-4'-bipyridinium dichloride), a fast-acting and broad-spectrum quaternary nitrogen herbicide, is widely used in the world, and this herbicide is highly toxic to humans and

animals (Sun et al., 2016) as it undergoes a redox cycling reaction that triggers reactive oxygen species (ROS) production and oxidative stress, leading to organ injury (Novaes et al., 2016). Epidemiological studies indicated PQ exposure as a potential risk factor for the onset of Parkinson's disease (Berry et al., 2010). Cases of PQ intoxication in humans are often related to suicide (Bismut and Hall, 1995). Therefore, PQ is a banned substance in the European Union, and the US environmental Protection Agency (EPA) has included PQ in a priority list of hazardous chemicals

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(US EPA, 1989). PQ is polar, highly soluble in water and has low volatility. Owing to its extensive use, PQ may enter surface water via spray drift, leach from soil and water, or run off from agriculture (Moustakas et al., 2016). Fernández et al. (1998) reported that the PQ concentrations in the irrigation channels, rivers, and lagoons water bodies of the Valencian community (Spain) covered a range of 0.01–3.95 mg L⁻¹. Moreover, Amondham et al. (2006) found that the concentrations of PQ in the Thailand ground and surface water bodies covered a range of 1.5–18.9 mg L⁻¹ and 9.3–87.0 mg L⁻¹, respectively, which are higher than the drinking water limits recommended by the EPA (3 µg L⁻¹) (US EPA, 1989). Therefore, the present of the PQ residue in a body of water may threaten the survival of fish.

In recent years, the adverse effect of PQ on fish has received substantial attention. There have been a few reports on the toxicity of PQ in fish, such as histological alterations induced by PQ exposure in gourami fish (Banaee et al., 2013) and common carp (Ma et al., 2014a); biochemical toxicity on common carp (Nemcsók et al., 1984; Matkovics et al., 1987; Asztalos et al., 1988) and African catfish (Ayanda et al., 2015); oxidative stress in spotted snakehead (Parvez and Raisuddin, 2006), Nile tilapia (Figueiredo-Fernandes et al., 2006a, 2006b), and zebrafish (Wang et al., 2016); effects on the pentosephosphate shunt and thiamine levels of rainbow trout (Akerman et al., 2003); effects on the behaviour of *Oreochromis niloticus* (Babatunde and Oladimeji, 2014) and zebrafish (Nunes et al., 2017); and effects on embryo toxicity of zebrafish (Ling et al., 2017). In previous studies, we preliminarily researched the immunotoxicity of PQ on common carp, and the results revealed that PQ-exposure altered some cytokine (interleukin-1β (IL-1β), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α)) levels, lysozyme (LYZ) activities, immunoglobulin M (IgM) and complement 3 (C3) contents in the liver, kidneys, or spleen of common carp and caused remarkable histopathological damage in fish organs (Ma et al., 2014a, 2014b), but information on the effect of PQ on hepatic detoxification and hepatotoxicity is still scarce.

Fish species are widely used as bio-indicators of the environmental levels of anthropogenic pollutants because they are highly sensitive to the presence of chemicals in various aquatic ecosystems (X.Y. Li et al., 2013; X. Li et al., 2013; Xing et al., 2012; Ma and Li, 2015; Moyson et al., 2016). The position of fish is at the top of the aquatic food chain, and they are more vulnerable when the poisons reach the trophic web by biomagnifications; therefore, the use of these fishes as food represents a risk to human health (Abdel-Moneim et al., 2012). Common carp (*Cyprinus carpio* L.) is widely distributed freshwater fish and is used as an animal model for toxicological tests to determine the toxicity of pesticides in aquatic environments (X.Y. Li et al., 2013; X. Li et al., 2013; Xing et al., 2012; Sehonova et al., 2017). The liver plays a pivotal role in the metabolism of various xenobiotics and has a high potential for generating ROS, and thus, the liver is at high risk for toxic damage (Hinton and Lauren, 1990; Lattuca et al., 2009). In fact, the liver has been regarded as an important target of PQ poisoning (Malekinejad et al., 2010; Ma et al., 2014a).

In the present study, carp liver were adopted to investigate changes of metabolism-related enzymes, oxidative stress parameters, inflammatory cytokines, and apoptosis indicators to reveal the possible mechanism of metabolism and hepatotoxicity in the fish liver caused by PQ exposure. The results of the study will further the current understanding of the hepatic detoxification and hepatotoxicity mechanisms affected by PQ exposure in fish.

2. Materials and methods

2.1. Paraquat and reagents

Paraquat (PQ, 1-1'-dimethyl-4-4'-bipyridinium dichloride) as a commercial formulation (200 g L⁻¹, w/v) was obtained from Anhui Fengle Agrochemical Co., Ltd. China. PQ was first dissolved in double-distilled water for use as a stock solution and then diluted with dechlorinated tap water to obtain the experimental concentrations. Other reagents were of analytical grade and were purchased from commercial sources.

2.2. Experimental fish

Common carp (8.14 ± 1.37 g) were originally purchased from a local fish farm (Feilong Aquarium Fishery, Xinxiang, China). The domesticated conditions of the fish have previously been described (Ma et al., 2014a). In brief, fish were subjected to a prophylactic treatment by bathing twice in 0.05% potassium permanganate for 2 min before raising them in a 200-L tank under lab conditions for at least two weeks before testing. The following quality characteristics of the water were used: total hardness of water, 340 mg L⁻¹; pH, 7.6; turbidity, 1.5 NTU; total dissolved solid, content 660 mg L⁻¹; and dissolved oxygen values, 7.0 mg L⁻¹. Fish were maintained at 25 ± 2 °C and exposed to a 16 h light/8 h dark photoperiod, and the tank water was partially changed every day with aerated tap water. During acclimatization, the fish were fed with commercial food from the Feilong Aquarium Fishery at a day-rate of 1–1.5% of fish body weight. The present study was conducted under the strict control of the China Law for Animal Health Protection and Instructions for Granting Permits for Animal Experimentation for Scientific Purposes (Ethics approval No. SCXK (YU) 2005-0001).

2.3. PQ exposure and sampling

Based on the LC₅₀ value obtained by the acute toxicity test as previously described (Ma et al., 2014a), PQ concentrations of 0, 1.596 (1/10 of 72 h-LC₅₀), and 3.192 mg L⁻¹ (1/5 of 72 h-LC₅₀) were used for sub-acute exposure of common carp, with 18 fish in each of the above treatments, and the experimental conditions were previously described according to Ma et al. (2014a). In brief, the fish were exposed to PQ solution under a semi-static condition for 7 d, and no food was provided to avoid interference or adverse effects on the following biochemical assay owing to the difference in ingestion and digestion between the treatment group and control group fish; however, saturated oxygen was maintained for fish. The water and PQ solution were completely changed every day. All experiments were performed in triplicate, and no fish death was observed during the experimental period.

Table 1
Specific primers used for qPCR in the present study.

Primers	Sequences	Gene no.
CYP1A	F: 5'-ATTTCATTCCCAAGACACCTG-3' R: 5'-CAAAAACCAACACCTCTCTCC-3'	AB048939
CYP2K	F: 5'-GCTCTTCCTGTCTTC-3' R: 5'-TGTGACTTCTACTACTC-3'	GU046696
CYP3A138	F: 5'-GACCTTCGCCCTCCACAG-3' R: 5'-CCTCATCCCGATGCAGTTC-3'	KF790756
GSTa	F: 5'-TACAATACTTTACGCTTTCCC-3' R: 5'-GGCTCAACACCTCCTTCAC-3'	DQ411310
GSTpi	F: 5'-GTCCTTTGCTCTGCCCTCTCTG-3' R: 5'-TTACTGCTTCCCATTCGCAATTG-3'	DQ411313
MDR1	F: 5'-TTGGGCTGTGGGAAGAG-3' R: 5'-GTGGATGTTTCAGTTGCTTTGTG-3'	AY999964
HSP70	F: 5'-GGCAGAAGGTGACAAATGCA-3' R: 5'-TGGGCTCGTTGATGTTCTCA-3'	AY120894
HSP90	F: 5'-GGCTACCAATCACTCTCTTCGT-3' R: 5'-GGGTTTGCTCTCGCTTCCT-3'	AF170296
iNOS	F: 5'-TGGTCTCGGGTCTCGAATGT-3' R: 5'-CAGCGCTGCAACCTATCATC-3'	AJ242906
IL-6	F: 5'-GATTGGTACAACGAAGA-3' R: 5'-GCATGACCATATATGACCA-3'	AY102632
IL-8	F: 5'-GTCTTAGAGGACTGGGTGA-3' R: 5'-ACAGTGTGAGCTTGAGGGA-3'	DQ453125
IL-10	F: 5'-GCTGTCACGTCATGAACGAG-3' R: 5'-CCCCTTGAGATCTGAAATAT-3'	AB110780
TGFβ	F: 5'-ATCCTGTGGAGGAGGAATAC-3' R: 5'-CTGGAACCTGTGTATGAGC-3'	AF136947
β-Actin	F: 5'-GCTATGTGGCTCTTGACTTCG-3' R: 5'-CCGTGAGGAGCTGATAGCT-3'	M24113

F, forward, R, reverse.

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