Environmental Toxicology and Pharmacology 89 (2022) 103786

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

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

Indole-3-propionic acid mitigates chlorpyrifos-mediated neurotoxicity by modulating cholinergic and redox-regulatory systems, inflammatory stress, apoptotic responses and DNA damage in rats

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ARTICLE INFO

Keywords:
Chlorpyrifos
Indole-3-propionic acid
Acetylcholinesterase
Redox-regulatory systems
8-hydroxy-2′-deoxyguanosine

ABSTRACT

This study probed the neuroprotective influence of indole-3-propionic acid (IPA) in rats exposed to chlorpyrifos (CPF) alone at 5 mg/kg body weight or co-administered with IPA at 12.5 and 25 mg/kg for 14 days. Behavioral data indicated that IPA significantly ($p < 0.05$) abated CPF-mediated anxiogenic-like behaviors with concomitant improvement in the locomotor and exploratory behaviors as substantiated by track plots and heat maps data. Also, IPA mitigated CPF-mediated diminution in cholinergic and antioxidant defense systems whereas it markedly improved thioredoxin level and thioredoxin reductase activity in cerebral and cerebellar tissues of the animals. Co-administration of IPA significantly enhanced anti-inflammatory cytokine, interleukin-10 but suppressed oxidative and inflammatory stress, caspase-9 and caspase-3 activation with concomitant reduction in 8-hydroxy-2′-deoxyguanosine (8-OHdG) level and histological damage. Collectively, IPA-mediated neuroprotection involves modulation of cholinergic and redox-regulatory systems, inflammatory stress, apoptotic responses and DNA damage in cerebrum and cerebellum of rats.

1. Introduction

Chlorpyrifos (CPF) is an organophosphorus pesticide extensively deployed in agricultural, gardening and industrial sectors globally owing to its efficacy (Burke et al., 2017, Foong et al., 2020). Although the home usage of CPF has been banned, its indiscriminate application in non-residential areas has been verified to be toxic to non-target species via inhalation, dietary ingestion and dermal exposure (Giesy et al., 2014; Ubaid-Ur-Rahman et al., 2021). The frequent detection of CPF on the surfaces of grains, fruits, vegetables and water courses poses a great health risk to both human and wildlife (**Del Prado-Lu et al., 2015,** European Food Safety Authority, 2018, Sang et al., 2020). Epidemiological data indicated that CPF is a potent environmental risk factor for the development of neurological disorders. For instance, prenatal CPF exposure caused significant mental and motor deficiencies in children (Bouchard et al., 2011, Burns et al., 2013, Stein et al., 2016) whereas long-term occupational exposure to CPF is linked to behavioral deficits in adult pesticide workers (Anger et al., 2020).

Exposure of experimental animals to sub-lethal CPF doses during early life caused marked impairment in psychomotor reflexes development, cognitive performance and sexual-social behaviors later in life (Lan et al., 2017, Berg et al., 2020, Perez-Fernandez et al., 2020). The potential of CPF to cross the blood-brain barrier has been associated with vulnerability of the brain to free radicals and consequently, alterations in morphological and function of nervous system (Li and Ehrich, 2013, Dominah et al., 2017, Adedara et al., 2018). Earlier investigations revealed that CPF elicits its noxious effects largely through its active metabolites CPF oxon which inhibits cholinergic neurotransmission and consequently, results in neurotoxicity both in rodents and humans (Gao et al., 2017, Imaishi and Goto, 2018). Excessive exposure to CPF reportedly causes acetylcholinesterase (AChE) inhibition and neuro-inflammation which are fundamental to the development of neurodegenerative disorders. Besides, CPF mediated toxicity is associated with reduced antioxidant capacity, elevated reactive oxygen and nitrogen species (RONS), inflammation and lipid peroxidation levels which are acknowledged indices capable of triggering apoptosis (Ki

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https://doi.org/10.1016/j.etap.2021.103786
Received 31 July 2021; Received in revised form 13 October 2021; Accepted 7 December 2021
Available online 13 December 2021
1382-6689/