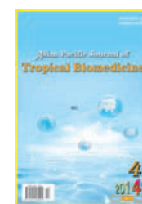


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Effects of melatonin on changes in cognitive performances and brain malondialdehyde concentration induced by sub-chronic co-administration of chlorpyrifos and cypermethrin in male Wistar rats

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PEER REVIEW

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Comments

This is a good study in which the authors evaluated the toxic effects of CPF and CYP and the protective role of melatonin as an antioxidant.
Details on Page 322

ABSTRACT

Objective: To evaluate the ameliorative effect of melatonin on sub-chronic chlorpyrifos (CPF) and cypermethrin (CYP)-evoked cognitive changes in male Wistar rats.

Methods: Fifty adult male Wistar rats, divided into five groups of ten rats each, were used for the study. Groups I and II were given distilled water and soya oil (2 mL/kg) respectively. Group III was administered with melatonin at 0.5 mg/kg only. Group IV was administered with CPF [7.96 mg/kg (1/10th LD₅₀)] and CYP [29.6 mg/kg (1/10th LD₅₀)] , and Group V was administered with CPF [7.96 mg/kg (1/10th LD₅₀)] and CYP [29.6 mg/kg (1/10th LD₅₀)] 30 min after melatonin (0.5 mg/kg). The regimens were administered by gavage once daily for 12 weeks. Thereafter, cognitive performances were determined and the brain was evaluated for malonaldehyde concentration.

Results: CPF and CYP induced cognitive deficits and increased brain malonaldehyde concentration, which were all ameliorated by melatonin.

Conclusion: Cognitive deficits elicited by CPF and CYP was mitigated by melatonin due to its antioxidant property.

KEYWORDS

Chlorpyrifos, Cypermethrin, Cognition, Brain malondialdehyde, Melatonin

1. Introduction

The application of pesticides, which plays a pivotal role in the control of vector-borne crop diseases, has resulted in tremendous increase in crop production and, consequently, meeting the food demand of the escalating global human and animal population. Unfortunately,

most of the applied pesticides are dispersed in the environment[1], and they adversely affect the health of both humans and animals[2,3]. The application of combined pesticides with different modes of action is fast gaining popularity in pest control programmes because such applications result in manifestation of broad spectrum of activity, with better efficacy in pest control[4]. Thus, the

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combination of pesticides exhibits a different toxicological profile, when compared with the toxicity of the individual pesticides in the combination[4]. Concurrent exposure to chlorpyrifos (CPF) and cypermethrin (CYP) leads to the inhibition of esterases, responsible for hydrolysis of the latter and, consequently, slows down its metabolism[5]. Such interaction enables the use of smaller doses of both pesticides[6]. Although beneficial in combating pest resistance, the formulations of combined pesticides pose a new challenge to human and animal health since the outcomes of such interactions are unknown. CPF [O,O-diethyl-O-(3,5,6-trichloro-2-pyridyl) phosphorothionate] is a broad-spectrum organophosphate insecticide utilized extensively in agriculture and for residential pest control throughout the world[7].

Chlorpyrifos is one of the most widely used organophosphate insecticides in agriculture and public health, despite restrictions placed on some of its domestic uses by United States Environmental Protection Agency in 2000. It is an irreversible inhibitor of acetylcholinesterase in the central and peripheral nervous systems that causes accumulation of acetylcholine, which in turn results in neurotoxicity in animals and humans[8]. The nervous system is the primary target because acetylcholinesterase catabolizes acetylcholine, thereby terminating its synaptic function[8]. Oxidative stress is one of the mechanisms implicated in CPF-evoked neurotoxicity[9,10].

CYP is a pyrethroid insecticide, which acts as a stomach and contact insecticide, and it is widely used in the production of cotton, cereals, vegetables and fruits, for food storage, in public health and animal husbandry. Its structure is based on pyrethrum, a natural insecticide which is contained in chrysanthemum; but it has a higher biological activity, and is more stable than its natural model[11]. The main mechanism of CYP is through its interference with sodium channels in nerve cells, by delaying its closure, which results in repetitive firing and eventually impairment of neuronal transmission[12]. Furthermore, CYP induces oxidative damage by increasing lipid packing and decreasing membrane fluidity in cells. It decreases the activity of glutathione peroxidase[13].

Melatonin (N-acetyl-5-methoxytryptamine) is a potent antioxidant hormone secreted by pineal gland. The function of this indole amine, as a free-radical scavenger, is facilitated by the ease, with which it crosses morphophysiological barriers like blood-brain barrier, intracellular and subcellular barriers[14]. Umosen *et al.* showed that melatonin ameliorated the subacute CPF-induced oxidative changes in the testes and pituitary

glands[15]. Melatonin is also effective in protecting nuclear DNA, membrane lipids, and possibly, cytosolic proteins from oxidative damage. Melatonin, associated with the cellular antioxidant defence[16], acts at two levels: firstly, as a direct antioxidant, due to its ability to act as a free-radical scavenger; and secondly as an indirect antioxidant, since it is able to induce the expression and/or the activity of the main antioxidant enzymes[16].

The aim of the present study was to investigate the effect of exposure to a combination of CPF and CYP for 12 weeks on cognitive performance in male Wistar rats.

2. Materials and methods

2.1. Experimental animals

Fifty adult male Wistar rats obtained from the laboratory animal house of the Department of Veterinary Physiology and Pharmacology, Ahmadu Bello University, Zaria, Nigeria served as subjects. They were housed in cages in the Department of Veterinary Physiology and Pharmacology laboratory, Ahmadu Bello University, Zaria, Nigeria. The rats were given access to pellets, prepared from growers' mash, maize bran and groundnut cake at the ratio of 4:2:1, and water *ad libitum*. They were pre-conditioned for two weeks prior to the commencement of the experiment.

2.2. Chemical acquisition and preparation

Commercial grade CPF (Sabero Organics Gujarat Limited, India) and CYP (Jiangsu Yangnong Chemical Co. Limited, China) were obtained. They were reconstituted in soya oil (Grand Cereal and Oil mills Limited, Jos, Nigeria) to appropriate working concentrations. Melatonin tablet (3 mg, Nature Made Nutritional Products, Mission Hills, USA) was dissolved in 6 mL of distilled water to make 0.5 mg/mL suspension daily before administration.

2.3. Subchronic toxicity study

Fifty adult male Wistar rats aged 4 weeks were used for this phase of the study. They were divided by simple random selection into four groups of ten animals each. Rats in each group were weighed and marked on the tail with a board marker for identification. Group I (DW) was given distilled water while Group II (SO) were dosed with soya oil only at 2 mL/kg. Rats in Group III (MEL) was administered with melatonin (0.5 mg/kg)[9]. Rats in Group IV (CC) was co-administered with CPF (1/10th LD₅₀) and cypermethrin (1/10th

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