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EVALUATION OF MITOCHONDRIAL AND NEUROBEHAVIORAL DISORDERS IN BRAIN REGIONS OF OFFSPRING (F1, F2) AFTER GESTATING AND LACTATING FEMALE RATS EXPOSURE TO LOW-DOSE OF IMIDACLOPRID AND CYPERMETHRIN

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ABSTRACT

The imidacloprid (IMID) and cypermethrin (CYP) pesticides are known to have neurotoxic effects and negative brain developmental consequences when used separately, but little is known about the consequences of using them as a mixture. That could be passed down from one generation to the next. In this context, we were interested in studying the effect of oral exposure of female rats during gestation and throughout the lactational period to real doses of IMID (1.2 mg/kg) and CYP (6.7 mg/kg) either alone or in a mixture on behavior and mitochondrial redox status. The first and second generation pups were followed from birth to juvenile age using a series of tests to assess reflex, coordination and general motor function, including surface righting, cliff aversion, negative geotaxis and the muscle strength test. At PND 21, cholinergic function, oxidative stress and mitochondrial integrity were assessed in the striatum and hippocampus. Our results showed that IMID and CYP, alone or in combination, induced decreased body weight gain, impaired neurobehavioral performance, and AchE inhibition. Oxidative stress markers including GSH level and SOD, CAT, GST and GPx activities showed a significant decrease. While, lipid peroxidation which was assessed by MDA assay, cytosolic calcium level, swelling and mitochondrial permeability recorded a significant increase. In conclusion, the disruption of mitochondrial redox homeostasis and the presence of neurobehavioral disorders even in the offspring of the F2 generation suggests that independent and combined exposure to IMID and CYP during a critical period of development has irreversible effects; long-lasting and persistent.

Keywords: Imidacloprid, Cypermethrin, Neurobehavior, Striatum, Hippocampus, Mitochondria, Oxidative stress, Rats

INTRODUCTION

The fetal period and early life are important stages when optimal brain development is assured. This is when the basic structure of the brain is built. This construction involves a series of processes that are particularly vulnerable to chemical stressors including pesticides. Impairment of this process could disrupt homeostasis, thereby increasing the risk of neurodegenerative disorders **(Sunyer and Dadvand, 2019)**. Several studies have shown that exposure to pesticides is not only through inhalation, skin absorption or ingestion of contaminated food and water but also through the placenta and breast milk during critical periods of development **(Dewailly *et al*., 2014)**. The use of pyrethroids and neonicotinoids has registered a significant increase due to their efficiencies and wide range of application; they are also less toxic to non-target organisms and efficiently degradable. These two families are considered green pesticides compared to organophosphates. However, the effect of their low concentrations on wildlife, especially bees, as well as humans, remains of concern **(Zeljezic *et al*., 2017)**. The nervous system is the primary target of CYP, a pyrethroid that exerts a neurotoxic effect through voltage-gated sodium channels. Once this insecticide binds to the α subunit of the sodium channel, the latter remains in an open position, thus allowing a prolonged passage of sodium and a depolarization of the membrane and ends up disrupting neuronal transmission. Exposure to this pyrethroid also influences other channels such as voltage-gated calcium and potassium channels; it decreases dopamine and acetylcholine levels as it alters key enzymes involved in the synthesis and metabolism of neurotransmitters such as as adenosine triphosphatases and AChE **(Raszewski *et al*., 2016)**. In laboratory animals, intranasal exposure of mice to 5 and 20 mg/kg of CYP during gestation and lactation has been linked to mitochondrial dysfunction as a mechanism of developmental neurotoxicity **(Laugeray *et al*., 2017)**. Another study conducted on mice indicates that exposure to CYP results in the release of Ca2+ and free radicals leading to DNA damage and cell death **(Maurya, *et al*., 2014)**.

Neonicotinoids such as IMID act by binding to the α4 and β2 subunits of the nicotinic postsynaptic acetylcholine receptors (nAChRs) of mammals. The neurotoxicity of this class is manifested by the inhibition of acetylcholinesterase, thereby reducing the ability of this enzyme to break down acetylcholine in the synapses, which subsequently leads to continuous overstimulation of nerves and muscles. Prenatal exposure to its chemicals affects the formation of neural circuits in several regions of the brain that are involved in the regulation of depression, anxiety, memory and learning **(Sano *et al*., 2016)**.

Osaka *et al*., 2016 reported the presence of metabolites of the neonicotinoid Thiamotoxam in the urine of young children. The increased resistance of pests to a single pesticide application has made it necessary to use a cocktail of these chemicals in order to increase its speed of action **(Shittu *et al*., 2021)**. Therefore, the combined effect of this mixture can lead to a joint interaction between the chemicals thus altering the absorption, biotransformation, distribution and elimination of one on the other and subsequently causing the appearance of new metabolites which could be more dangerous in comparison with the basic preparation, which makes the question of the risk for ecology and human health even more serious **(Aouey *et al*., 2017)**.

To our knowledge, the CYP and IMID cocktail has not been studied for its transgenerational neurotoxic effects in mammals. Therefore, the objective of this study was to evaluate the toxicity of these pesticides alone or in mixture by examining their effects on neuromotor development, mitochondrial integrity and oxidative damage in the striatum and hippocampus of pups of generations F1 and F2 born to mothers (F0) exposed during gestation and throughout the lactation period.