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Inflammatory and oxidative mechanisms potentiate bifenthrin-induced neurological alterations and anxiety-like behavior in adult rats

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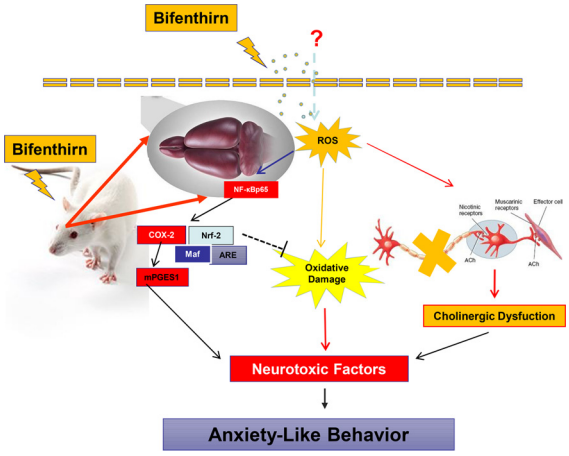
GRAPHICAL ABSTRACT

Graphical abstract summarizing the neurological alterations induced by BF. BF induces oxidative stress mediated inflammatory responses via the activation of Nrf2 and NF-kBp65 pathways in the striatum and frontal cortex, which promotes anxiety-alterations and cholinergic dysfunction.



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ABSTRACT

Bifenthrin (BF) is a synthetic pyrethroid pesticide widely used in several countries to manage insect pests on diverse agricultural crops. Growing evidence indicates that BF exposure is associated with an increased risk of

Abbreviations: BF, bifenthrin; AB, antibody; BCA, bicinchoninic acid; BW, body weight; CNS, central nervous system; COX, cyclooxygenase; IL, interleukin; mPGES, microsomal prostaglandin E synthase; Nrf2, nuclear erythroid-2 like factor-2; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PG, prostaglandin; SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; TNF, tumor necrosis factor; ROS, reactive oxygen species; MDA, malondialdehyde; GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; EPM, elevated plus maze; AchE, acetylcholinesterase; mAchR, muscarinic–cholinergic receptors; ChAT, choline acetyltransferase; OS, oxidative stress; AD, Alzheimer's disease; PD, Parkinson's disease; AL, allethtin; DM, deltamethrin

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developing neurodegenerative disorders. However, the mechanisms by which BF induces neurological and anxiety alterations in the frontal cortex and striatum are not well known. The present *in vivo* study was carried out to determine whether reactive oxygen species (ROS)-mediated oxidative stress (OS) and neuroinflammation are involved in such alterations. Thirty-six Wistar rats were thus randomly divided into three groups and were orally administered with BF (0.6 and 2.1 mg/kg body weight, respectively) or the vehicle (corn oil), on a daily basis for 60 days. Results revealed that BF exposure in rats enhanced anxiety-like behavior after 60 days of treatment, as assessed with the elevated plus-maze test by decreases in the percentage of time spent in open arms and frequency of entries into these arms. BF-treated rats also exhibited increased oxidation of lipids and carbonylated proteins in the frontal cortex and striatum, and decreased glutathione levels and antioxidant enzyme activities including superoxide dismutase, catalase and glutathione peroxidase. Treatment with BF also increased protein synthesis and mRNA expression of the inflammatory mediators cyclooxygenase-2 (COX-2), microsomal prostaglandin synthase-1 (mPGES-1) and nuclear factor-kappaBp65 (NF-kBp65), as well as the production of tumor necrosis factor-α (TNF-α) and ROS. Moreover, BF exposure significantly decreased protein synthesis and mRNA expression of nuclear factor erythroid-2 (Nrf2) and acetylcholinesterase (AChE), as well as gene expression of muscarinic–cholinergic receptors (mAchR) and choline acetyltransferase (ChAT) in the frontal cortex and striatum. These data suggest that BF induced neurological alterations in the frontal cortex and striatum of rats, and that this may be associated with neuroinflammation and oxidative stress via the activation of Nrf2/NF-kBp65 pathways, which might promote anxiety-like behavior.

1. Introduction

Many synthetic substances released into the environment were initially thought to be relatively harmless, but over time, scientists began to realize their adverse effects on the environment and human health, and their association with neurodegenerative diseases, such as Alzheimer (AD) and Parkinson (PD) (Lee et al., 2016; Yegambaram et al., 2015). Among the contaminants that are likely to disturb brain development and function, BF and other synthetic pyrethroid (SP) insecticides are highly relevant candidates given that the general population is extensively exposed to this family of pollutants through dietary intake and residential application in gardens and homes for pest-control purposes (Scollon et al., 2011; Blair et al., 2015; Morgan et al., 2016; Schettgen et al., 2002; Taetzsch and Block, 2013).

SPs, such as BF, are associated with developmental effects, immunological abnormalities, and neurotoxicity (DeMicco et al., 2010; Soderlund, 2012). The reported neurotoxic effects of BF and other pyrethroids are considered to be primarily mediated by their interaction with sodium channels, leading to membrane depolarization and hyperexcitability of neuronal cells (Cao et al., 2014; Neal et al., 2010; Soderlund et al., 2002; Verschoyle and Aldridge, 1980). This group of pesticides has also been shown to act on isoforms of voltage sensitive calcium channels, thereby contributing to the release of neurotransmitters and hence leading to induced toxicity (Cao et al., 2011; Soderlund, 2012; Yang and Li, 2015). The cholinergic system is another potential target for the action of SPs (Hossain et al., 2004). Interestingly, cholinergic neurons and their projections are widely distributed throughout the central nervous system (CNS) with an essential role in regulating many vital functions, such as learning, memory, cortical organization of movement, and cerebral blood flow control (Mesulam, 2004; Mesulam et al., 1983).

SP toxicity has been shown to inhibit AChE (Ansari et al., 2012; Kakko et al., 2003), with ensuing alteration of cholinergic neurotransmission, which can lead to cognitive alterations. In human epidemiological studies, occupational exposure to SPs has been associated with neuro-behavioral deficits and psychiatric disorders including anxiety and depression (Blair et al., 2015; David et al., 2009; Fiedler et al., 2015; Hossain et al., 2004; Wolansky and Harrill, 2008). In this regard, acute and long-term exposure to SPs has been associated with emotional disorders, such as anxiety/depression-like changes (Fiedler et al., 2015; Kung et al., 2015). However, the complete mechanisms by which BF induces anxiety-like behavior in rodents are unknown.

Other studies later revealed that noradrenergic, glutamatergic and cholinergic systems are also involved in the mechanisms leading to mental disorders such as anxiety, depression, alteration of learning and memory, and the pathophysiological processes underlying AD have been linked to disturbances in glutamate neurotransmission (Danysz and Parsons, 2012; Francis, 2003; Francis et al., 2012). Signal cascades triggered by the activation of postsynaptic NMDA receptors are fundamentally important for the regulation of behaviors related to anxiety and depression (Mineur et al., 2018). However, the impact of BF on cholinergic receptors, which play an important role in modulating behaviors related to stress response, anxiety, and depression as well as other behaviors, is not understood. Excitotoxicity effects induced by BF have been related to the overstimulation of glutamatergic receptors, suggesting that it induces an elevation of glutamate levels (Bagetta et al., 1992). Cognitive deficits following low level exposure to pyrethroids have also been observed in experimental studies in young animals (Ansari et al., 2012; Hossain et al., 2004; Nasuti et al., 2003).

Recent studies revealed that oxidative stress (OS) is associated with diverse chronic neurodegenerative diseases, such as PD or AD, usually leading to cognitive decline and neuronal loss (Liu et al., 2017; Zhou et al., 2015). Furthermore, chronic neuroinflammation is an essential factor accounting for neurodegenerative diseases (Allison and Ditor, 2015; Chung et al., 2006). Overexpression of pro-inflammatory cytokines, such as IL-1β and TNF-α, in the brain is considered to lead to neuronal damage and subsequent neuronal loss (Cannon and Greenamyre, 2011; Heneka et al., 2014a). It was reported that an activated OS response causes a downstream cascade of biological response, which involves activation of NF-kB and expression of other inflammatory mediators (Shi et al., 2003).

Thus, the aim of this study was to investigate the role of OS and inflammation in BF-induced neurological alterations in the frontal cortex and striatum of adult rats and to study the involvement of brain cholinergic receptors in BF-induced anxiety-like behavior.

2. Materials and methods

2.1. Chemicals

Technical-grade bifenthrin (BF) [2-methylbiphenyl-3-ylmethyl-(Z)-(1RS)-cis-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate, 99.5%] was purchased from Sigma-Aldrich (Sigma Aldrich, Deisenhofer, Germany) as well as all other chemical products used in this study.

2.2. Animals and treatments

Adult male Wistar rats weighing 250–300 g and of about 8 weeks old were purchased from the Central Pharmacy (SIPHAT, Tunisia). Animals were housed in polypropylene cages with clean chip bedding and maintained in air-conditioned animal houses under a 12/12 h light