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Review Article

Unifying Mechanism involving Neonicotinoids for Bee Toxicity: Electron Affinity, Nitrogen dioxide, Oxidative Stress, Reactive Oxygen Species

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Abstract

Various mechanisms have been advanced for bee toxicity resulting in declining numbers. This review provides evidence for a connection between use of neonicotinoids and decrease in bee population. Most attention is given to imidacloprid. The theory involves electron transfer, production of reactive oxygen species and oxidative stress. Calculations show that electron affinity is favorable for the protonated form of the pesticide. Also, rapid decomposition occurs to NO2, which may be the actual toxic material.

Keywords: Bee Toxicity; Electron Affinity; Reactive Oxygen Species; Oxidative Stress; Neonicotinoids; Imidacloprid; Thiamethoxam; Clothianidin; Nitrogen dioxide

Introduction

There has been much controversy involving a connection between use of neonicotinoids and declining bee populations. The pesticides receiving the most attention is Imidacloprid (IMD) (Figure 1), thiamethoxam (Figure1), and its breakdown product clothianidin (Figure 1). The focus of our attention is on IMD. A number of foreign countries have banned this class, and a ban is under consideration by the United States. As expected, some pesticides producers have challenged the bans, whereas others have voluntarily terminated use. In recent years, there has been increasing evidence for bee toxicity from this pesticide class [1-7]

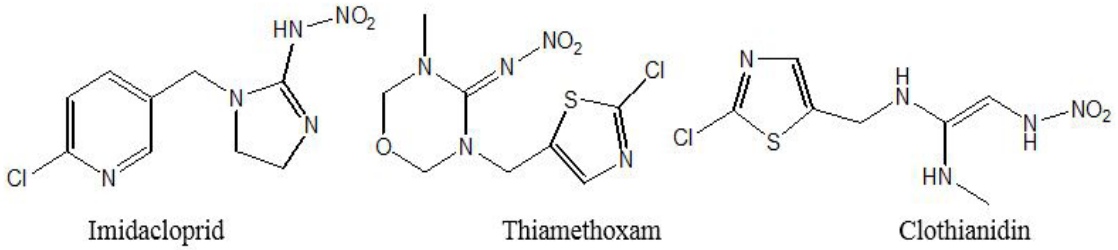
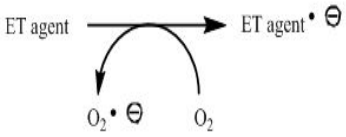


Figure 1: Structure of Imidacloprid, Thiamethoxam and Clothianidin.

"The preponderance of bioactive substances, usually as the metabolites, incorporates Electron Transfer (ET) functionalities. We believe these play an important role in physiological responses. The main group include quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or

iminium species). Resultant redox cycling is illustrated in Scheme 1. *In vivo* redox cycling with oxygen can occur, giving rise to Oxidative Stress (OS) through generation of Reactive Oxygen Species (ROS), such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide) (Scheme 2)" [8].



Scheme 1: Redox Cycling with Superoxide Formation.

Scheme 2: Generation of Reactive Oxygen Species.

In some cases, ET results in involvement with normal electrical effects (e.g., in respiration of neurochemistry). Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, (i.e., more positive than about -0.5 V). Hence, ET *in vivo* can occur resulting in production of ROS which can be beneficial in cell signaling at low concentrations, but produce toxic results at high levels. Electron donors consist of phenols, N-heterocycles or disulfides in proteins which produce relatively stable radical cations. ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins, (e.g., antiinfective agents [9], anticancer drugs, [10], carcinogens [11], reproductive toxins [12], nephrotoxins [13], hepatotoxins [14], cardiovascular toxins [15], nerve toxins [16], mitochondrial toxins [17], abused drugs [18], pulmonary toxins [8], ototoxins [19] and various other categories [20].

There is a plethora of experimental evidence supporting the ET-ROS theoretical framework. This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is consistent with the frequent observation that many ET substances display a variety of activities (e.g., multiple-drug properties), as well as toxic effects.

It is important to recognize that mode of action in the bio domain is often multifaceted. In addition to the ET-ROS-OS approach, other aspects may pertain, such as, enzyme inhibition, allosteric effects, receptor binding, metabolism and physical factors. A specific example, involves protein binding by quinones in which protein and nucleophiles, such as amino or thiol, effect conjugate addition" [21]. We calculated the Electron Affinity (EA) of imidacloprid using density functional calculations to determine, initially, the likelihood that the molecule could serve as an ET agent. The calculations were carried out using the B3LYP method and Dunning's augmented cc-pVDZ basis set, running under Gaussian 09 on a Linux cluster. Geometries for the negative anion, neutral molecule, and protonated cation were optimized individually to determine the EA of the neutral and protonated forms of the molecule. The EA for the neutral molecule was shown to be 0.82 eV, and the EA for the protonated cation was shown to be 6.70 eV.

The results from the calculations are listed in Table 1. The protonated form of the molecule was calculated with a multiplicity of 1, and the neutral form with a multiplicity of 2 to determine the electron affinity of the protonated molecule.

Compound	Energy (in eV)
Imidacloprid	0.821
Imidacloprid-H^+	6.696

Table 1: Calculated EA values of neutral and protonated Imidacloprid.

The value for the EA of the neutral molecule is greater than those of notable ET functionalities, such as quinones (0.54-0.64 eV) and aromatic nitro compounds (0.59 eV for dinitrophenol), revealing its potential to serve as a viable ET agent. EAs are predicted to be 1.63 eV and 1.30 eV for the conformers of amphotericin B [22]. Further calculations of the protonated form reveal that its EA is much higher than those of quinones and aromatic nitro compounds. This high value is due to the decomposition of the molecule to release NO2 when it is introduced to an electron.

Nitrogen dioxide

NO_2 is a ubiquitous air toxicant which induces damage to various organs including the lung [23]. Genes related to OS were strongly induced. The effects are associated with the oxidant properties. Inflammatory and AO responses were observed after exposure to NO_2 [24]. Lipid peroxidation, as measured by ethane formation, increased appreciably [25]. AO protective enzyme activities were complementary effects which protected cells from damage by the lipid peroxides. One of the proposed mechanisms of pulmonary injury involves peroxidation of membrane lipids [26,27]. In a study of toxic mechanism, lipid peroxyl radicals are generated in a radical-mediated peroxidation pathway [28]. During cell damage, there is breakdown of AO alpha-tocopherol. The AO glutathione showed appreciable change on exposure to NO2 [29]. The AO is known to protect erythrocytes from generated OS. Apparently, there has not been prior recognition of possible involvement of the metabolite NO2 in bee toxicity or in pesticide action in plants arising from neonicotinamides.

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