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Kumiai Chemical Industry Co., Ltd.

Clarification of the Mode of Action of a New Acaricide, Flupentiofenox

Kumiai Chemical Industry Co., Ltd. has revealed that the novel acaricide "Flupentiofenox", currently under pesticide registration application, exhibits acaricidal activity through a novel mode of action different from that of commercial acaricides.

The findings were published online in the “Journal of Agricultural and Food Chemistry” on August 7, 2024.

1. Research Background

Spider mites possess high reproductive capacity, short generation times, and potent detoxification metabolic activity, facilitating the development of pesticide resistance and making it challenging to protect crops. Therefore, developing acaricides with new modes of action is essential.

2. Features of Flupentiofenox

Flupentiofenox is effective against all developmental stages (eggs, larvae, and adults) of spider mites. Additionally, due to its unique mode of action, it is effective against spider mites that have developed resistance to existing acaricides.

3. Research Findings

This study revealed that flupentiofenox inhibits aerobic energy metabolism in the mitochondria of spider mites. Mitochondria are organelles responsible for cellular energy production, generating energy molecules called ATP (adenosine triphosphate). Glucose, fatty acids, and many amino acids are metabolized into acetyl-CoA, which enters the citric acid cycle. Subsequently, this cycle feeds into the respiratory chain, where a large amount of ATP is produced. Since oxygen is required for this ATP production, it is called aerobic energy metabolism (Figure 1).

In this study, we initially confirmed changes in ATP content in spider mites treated with flupentiofenox. As a result, a significant decrease in ATP content was observed following treatment with this agent (Figure 2A). Next, we examined which part of the aerobic energy metabolism pathway flupentiofenox inhibits to reduce ATP content, using changes in oxygen consumption linked to ATP production as an indicator. Specifically, we confirmed whether the acceleration of oxygen consumption upon the addition of pyruvate,

a common product of glucose and amino acid metabolism, or fatty acids to mitochondria changed with flupentiofenox treatment. As a result, the acceleration of oxygen consumption upon the addition of pyruvate did not change with or without flupentiofenox treatment (Figure 2B), whereas the acceleration of oxygen consumption upon the addition of fatty acids was suppressed by flupentiofenox treatment (Figure 2C). As shown in Figure 1, pyruvate and fatty acids are metabolized along the same pathway after being converted into acetyl-CoA. Therefore, the result that only the addition of fatty acids reduced oxygen consumption led to the conclusion that flupentiofenox specifically and strongly inhibits the fatty acid metabolic pathway (from the uptake of fatty acids into mitochondria to the production of acetyl-CoA via β-oxidation) in aerobic energy metabolism, thereby reducing ATP content (Figure 3). As a result, the spider mites fall into an energy deficit and die.

4. Practicality and Promise

Flupentiofenox is the first pesticide targeting the fatty acid metabolic pathway in mitochondrial energy metabolism. Commercial acaricides mainly target respiratory chain complexes and oxidative phosphorylation in energy metabolism. However, this new mode of action is effective against resistant spider mites. Therefore, Flupentiofenox, with its novel mode of action, offers a promising solution for managing phytophagous mites including multiple-acaricide resistant populations, providing a new approach for crop protection.

< Reference diagram >

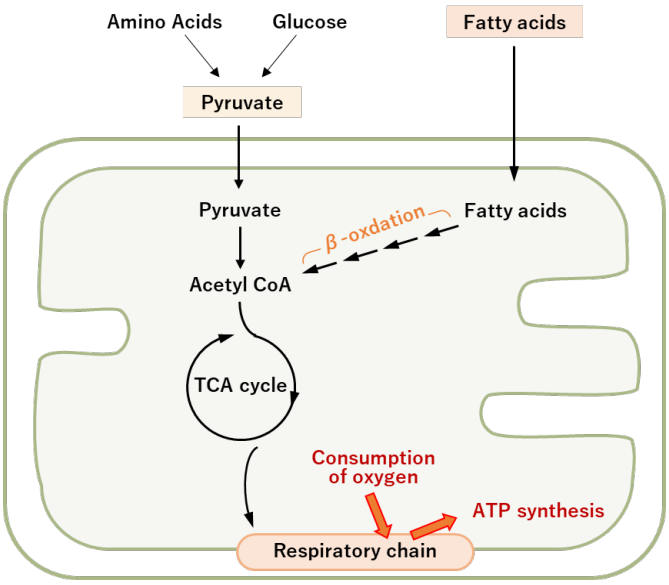

Figure 1. Aerobic energy metabolism in the mitochondria

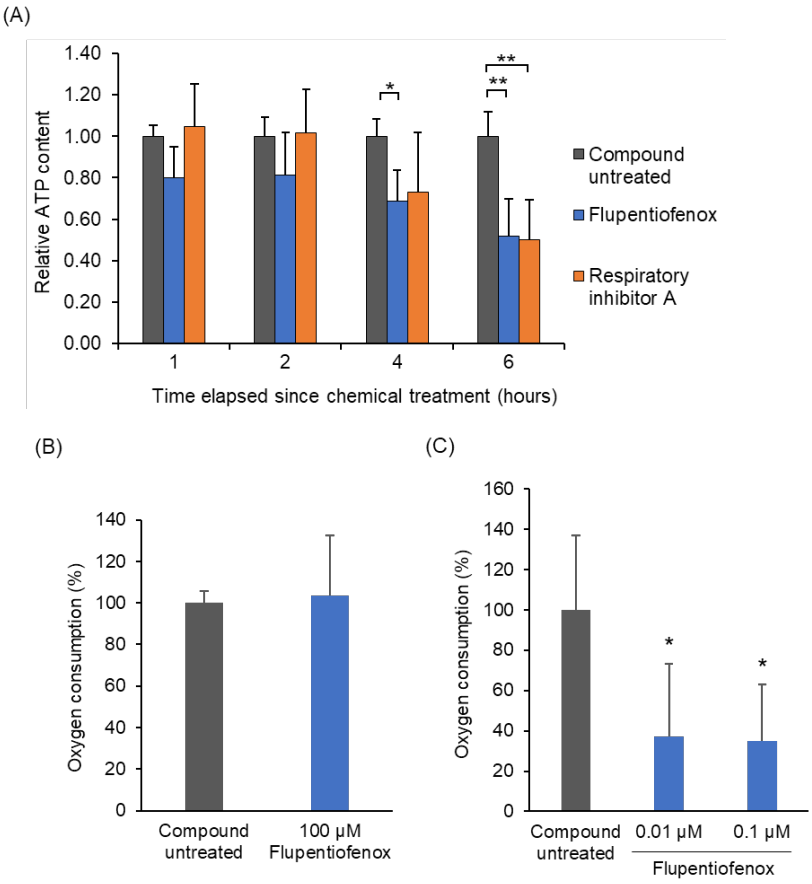

Figure 2. Effect of flupentiofenox

(A) Effect of flupentiofenox on the ATP content in spider mites

(B) Effect on the oxygen consumption under pyruvate supply condition

(C) Effect on the oxygen consumption under long-chain fatty acid supply condition

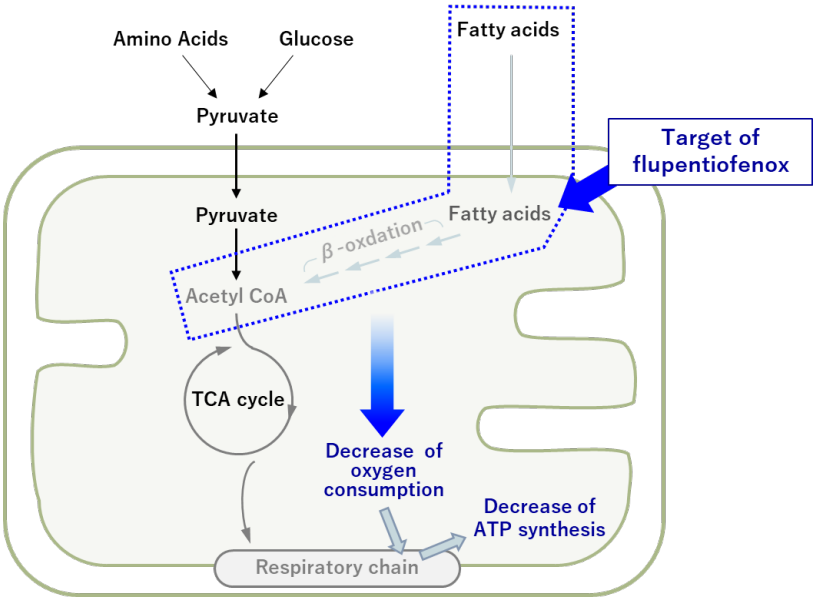

Figure 3. Target of flupentiofenox in the aerobic energy metabolism

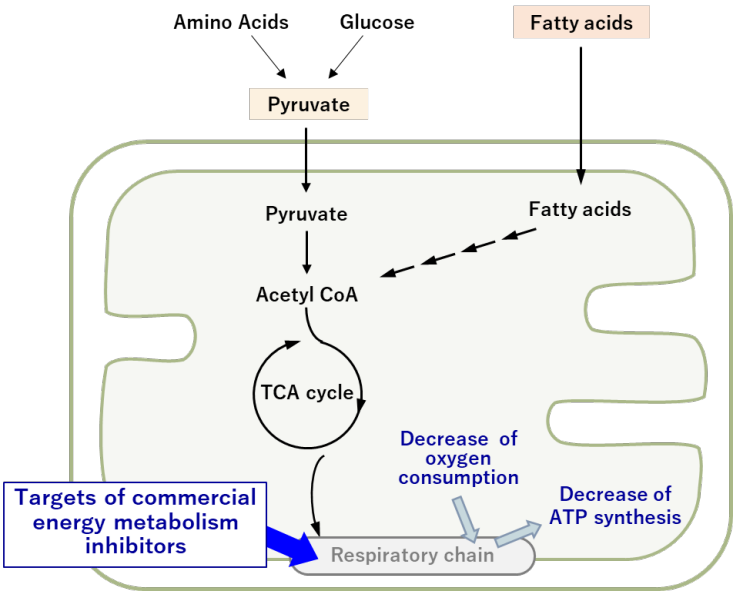

Figure 4. Targets of commercial energy metabolism inhibitors

<Glossary>

1. β-oxidation

The pathway that metabolizes fatty acids by removing two carbons at a time to produce acetyl-CoA. For example, palmitic acid, with 16 carbons, undergoes β-oxidation seven times to produce eight molecules of acetyl-CoA.

2. Respiratory Chain

The mitochondrial respiratory chain mainly comprises four complexes (Complexes I-IV) and ATP synthase. These complexes work together to produce large amounts of ATP. Mitochondria play a central role in cellular energy production, with the respiratory chain being a crucial mechanism. Several agents are known to act on the respiratory chain to exhibit miticidal activity.

<Information>

- Chihiro Uchiyama, Shingo Yoshimura, Shunsuke Yamamoto, Masahiro Ogawa, and Kiyoshi Kawai, " Acaricide Flupentiofenox Inhibits the Mitochondrial β-Oxidation Pathway of Fatty Acids", *J. Agric. Food. Chem.*
  DOI: https://doi.org/10. 021/acs.jafc.4c030761

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