Hepatic thyroid hormone transport and thyroid hormone metabolism interplay might be involved in fipronil-induced disruption of thyroid homeostasis

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Aims of the work

Fipronil, a widely used insecticide, is a thyroid disruptor in rat inducing a decrease in thyroid hormones (TH) concentrations in blood. This decrease proceeds from an increased elimination rate (clearance) of TH. The liver is the main organ involved in TH metabolic clearance. TH hepatic metabolism can be modulated by specific transporters involved in TH/metabolites cell trafficking. This study aimed at contributing to a better understanding of the molecular pathways and mechanisms that underline fipronil-induced thyroid disruption, a key issue to evaluate the relevance of rat data in terms of the danger of fipronil for human health. A special emphasis was put on potential interplay between TH liver transport and metabolism.

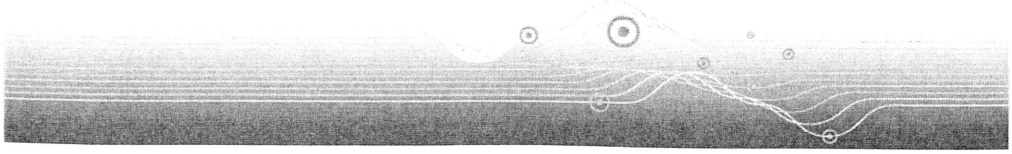
Methods

Experiment 1: Female rats were treated with vehicle (n = 14) or fipronil (3 mg/kg/d, n = 10 *per os* for 14 days). Livers were collected for microarray and RT-qPCR gene expression profiling.

Experiment 2: To determine if changes in gene expression could be of any functional significance, TH profiles (T_4, T_3 and T_2) were evaluated over 24 hours following an ip. administration of exogenous T4 (10 µg/kg) in thyroidectomized (THX) T3-treated (endogenous T4-free, T3: 10 µg/kg/d) Wistar female rats treated with fipronil (1.5 mg/kg/d per os for 14 days, n = 10) or vehicle. Plasma concentrations were measured by UPLC/MS/MS. Liver Ugt1a1 and Sult1b1 mRNA expressions and activities were measured. In addition, the impact of fipronil-treatment on the profiles of TH metabolites was evaluated in thyroid intact rats.

Key results

Experiment 1: Fipronil treatment was associated to a significant increase in the expression of genes coding for the hepatic phase II enzymes *Ugt1a1*, *Sult1b1* and *Gstα2* and for the transporters *Mrp2*, *Mrp3*, *Abcg5*, *Abcg8*, *Oatp1*, *Oatp2*, *Oatp4* and *Bsta1*. Some of these genes are clearly involved in thyroid hormone uptake into the hepatocytes (*Oatp1*, *Oatp2*), native and TH and their metabolites conjugation (*Ugt1a1*, *Sult1b1*) or elimination into the



bile (*Mrp2*). mRNA expression of the deiodinases (DOI) 1 and 3 were not significantly modified by fipronil treatment.

Experiment 2: Following exogenous T4 administration to THX+T3 rats, T_4, T3 and T2 plasma concentrations were higher in the vehicle group than in the fipronil-treated one for each time point. Unlike T_4 and T_3, T_2 plasma concentrations did not seem to vary following exogenous T4 administration. As in experiment 1 and despite the lower dose, liver mRNA expressions of the *Ugt1a1* and *Sult1b1* and UGT1A activity were increased in fipronil-treated group. Treatment had no effect on phenol SULT activity toward 2-naphtol.

In thyroid intact rats, fipronil daily treatment was associated to a significant decrease in T_4 and T_3 plasma concentrations. For the other quantifiable metabolites (T2 and MIT and DIT), no significant treatment effect was observed.

Conclusions

Overall all the suggested mechanisms could occur in the human liver. Most of the up-regulated pathways are targets of xenosensor nuclear receptors (XNRs). Demonstrating the implication of those receptors is important to understand fipronil mechanisms of action. Because XNRs exhibit huge interspecies variability of their pharmacological properties, they could be a key issue in evaluating the relevance of the rat model to evaluate the danger of fipronil for human health.

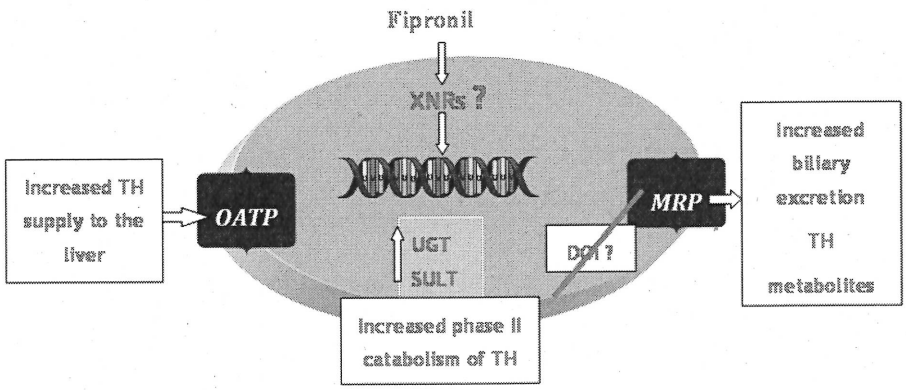


Fig.1 Hypothetical network between TH liver trafficking and metabolism mediating fipronil-induced thyroid disruption in the rat

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