**Topic:** INHIBITION OF TH RECEPTOR-MEDIATED TRANSCRIPTION BY ATDs

**Title:** Antithyroid drugs inhibit thyroid hormone receptor-mediated transcription.

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**SUMMARY**

**Context:** Methimazole (MMI) and propylthiouracil (PTU) are widely used as antithyroid drugs (ATDs) for the treatment of Graves’ disease. Both MMI and PTU reduce thyroid hormone levels by several mechanisms, including inhibition of thyroid hormone synthesis and secretion. In addition, PTU decreases 5’-deiodination of T4 in peripheral tissues. ATDs may also interfere with T3 binding to nuclear thyroid hormone receptors (TRs). However, the effect of ATDs on the transcriptional activities of T3 mediated by TRs has not been studied.

**Objective:** The present study was undertaken to determine whether ATDs have an effect on the gene transcription regulated by T3 and TRs in vitro.

**Methods:** Transient gene expression experiments and GH secretion assays were performed. To elucidate possible mechanisms of the antagonistic action of ATDs, the interaction between TR and nuclear cofactors was examined.

**Results:** In the transient gene expression experiments, both MMI and PTU significantly suppressed transcriptional activities mediated by the TR and T3 in a dose-dependent manner. In mammalian two-hybrid assays, both drugs recruited one of the nuclear co-repressors, nuclear receptor co-repressor, to the TR in the absence of T3. In addition, PTU dissociated nuclear co-activators, such as steroid receptor co-activator-1 and glucocorticoid receptor interacting protein-1, from the TR in the presence of T3. Finally, MMI decreased the GH release that was stimulated by T3.

**Conclusions:** ATDs inhibit T3 action by recruitment of transcriptional co-repressors and/or dissociation of co-activators. This is the first report to show that ATDs can modulate T3 action at the transcriptional level.

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**COMMENT**

The primary effect of antithyroid drugs (ATD: PTU & MMI) is to inhibit thyroid hormone synthesis by interfering with thyroperoxidase (TPO) mediated iodination of tyrosine residues in thyroglobulin. Other effects of ATDs include a reduction in the intra-thyroidal immune dysregulation and, in the case of PTU only, in peripheral conversion of T4 to T3. Until now, the extrathyroidal effects of ATDs have been feared rather than desired, since undesired side effects of ATDs are caused by the extrathyroidal effects of these drugs. Side effects include minor cutaneous reactions but also the more severe ‘antithyroid’ arthritis.
syndrome and even life-threatening complications such as agranulocytosis.

In present study, Moriyama et al. provide data in favour of some beneficial extrathyroidal effects of antithyroid drugs. After administration of antithyroid drugs, an immediate decrease in the O$_2$ consumption (prior to the decrease of serum T$_4$ or T$_3$) has been described previously, and an immediate inhibition of transcription of the uncoupling protein-3 (UCP3) has been proposed as the underlying mechanism. In a series of in vitro experiments, Moriyama et al. demonstrate an impairment of thyroid hormone action by ATDs (in pharmacological dosages), either by recruitment of repressors to the thyroid hormone receptor (TR), or by dissociation of co-activators from the TR. In the last experiment using GH3 cells (derived from a rat pituitary tumor cell line), the stimulation of GH release by T$_3$ was reduced after the addition of MMI.

The authors conclude that the finding “might be helpful in designing new therapeutic compounds with modifications of existing antithyroid drugs to enhance transcriptional inhibition against T$_3$ action”. In other words, the antithyroid drugs could be the short-track to the development of long awaited thyroid hormone antagonists. One more hypothesis: if the peripheral antithyroid action of ATDs is confirmed by other studies, and if it would remain sustained in the presence of another peripheral thyroid hormone antagonist (such as amiodarone), the antithyroid drugs might not be useless in the treatment of amiodarone-induced thyroiditis. Or is there still a place for a combined glucocorticoid and ATD treatment in this serious medical condition?

(Annick Van den Bruel, MD)

See Figure below

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**FIG. 7.** The inhibitory effects of ATDs on the GH secretion induced by T$_3$. GH3 cells were incubated with or without 1 nm T$_3$ and/or 10 $\mu$M MMI for 48 h. Culture media were collected and GH was measured by ELISA. *, $P < 0.05$. 

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