QST Model for the Hypothalamic-Pituitary-Thyroid Axis in Rat and Human

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Background

Certain chemicals, such as pharmaceuticals as well as agrochemicals may disrupt the hypothalamic-pituitary-thyroid (HPT) axis leading to thyroid toxicity if the exposure is sufficiently high. Disruption of the HPT axis manifests itself in alterations of TSH, T_4 and/or T_3 levels and the quantitative relationships between thyroid hormone levels and thyroid toxicity were reported in the literature [1]. Here we report a quantitative system's toxicology (QST) model to support thyroid toxicity assessment in rat and human

Methods

Based on published data for thyroid hormones, physiologically based kinetic (PBK) models for T_3, T_4 and TSH were developed in PK-Sim® [2]. PBK models for individual hormones were then extended in MoBi® [2] to include regulatory feedbacks and interconversions between the thyroid hormones (Figure 1). Importantly, structurally compatible models were developed in parallel for rat and human and parameterised to reproduce species-specific changes in thyroid hormone levels after administration of thyroid disrupting chemicals (TDCs).

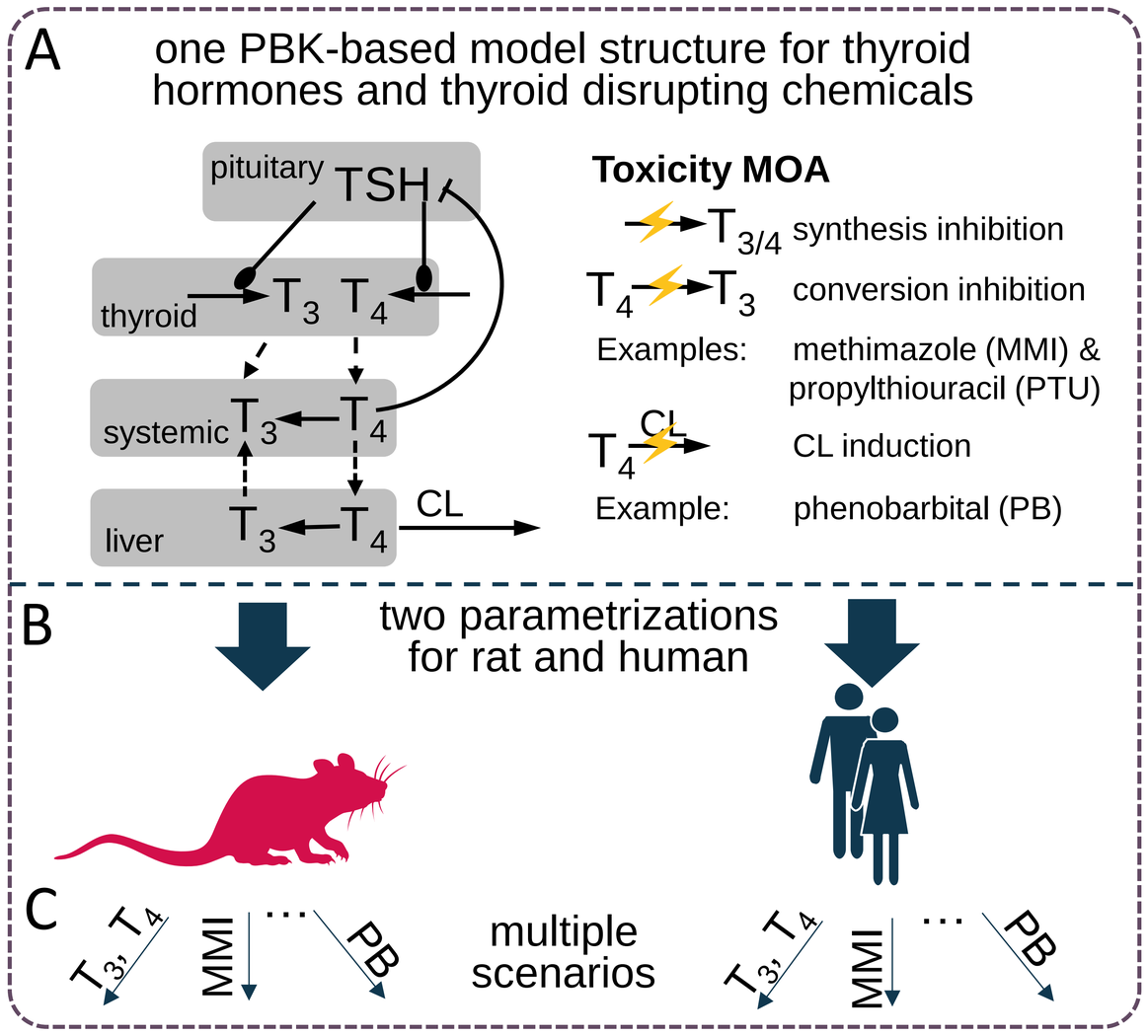
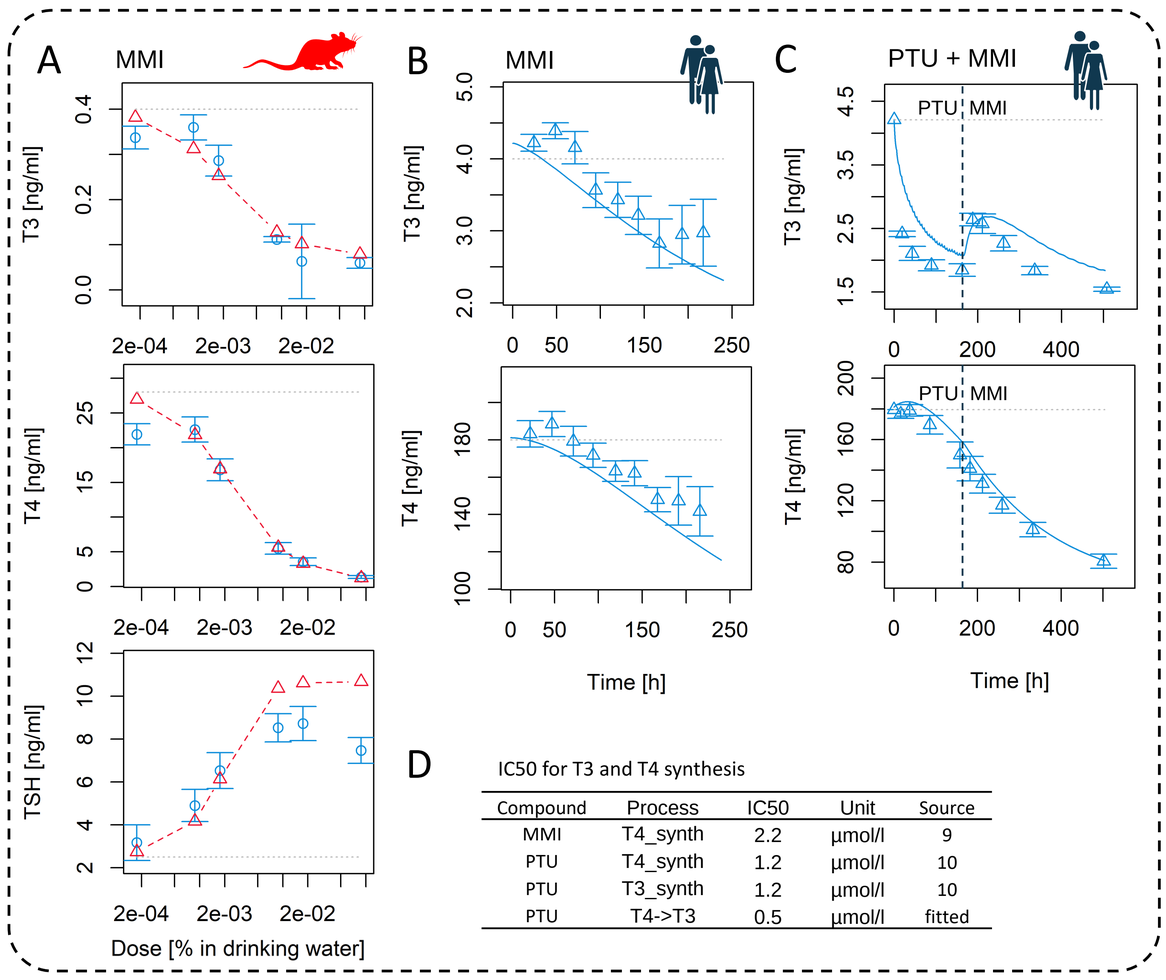


Figure 1. Model structure and model development approach. (A) QST model structure is consistent between rat and human. (B) Two specie-specific parameterisations are introduced to capture differences in rat and human HPT axis. (C) Multiple scenarios implemented to achive robust model parameterisation.

Results

The QST model adequately captures T_3, T_4 and TSH baseline levels and their kinetics after intravenous and/or oral T_3 and T_4 administration in both rat and human. The QST model also adequately recapitulates dose and time-dependent decreases in T_3 and T_4 levels and the compensatory increase in TSH levels after administration of direct-acting TDCs: methimazole (MMI) and propylthiouracil (PTU) (Figure 2 A and B). Furthermore, the model adequately captures the gradual decrease in T_4 levels and the peak in T3 levels after a switch from PTU to MMI treatment in human patients based on MMI and PTU in vitro IC50 values for T_3/T_4 synthesis inhibition (Figure 2 C and D). The model also recapitulates a change in thyroid hormone levels induced by indirect TDCs, namely an increase in T_4 clearance in a rat model as observed after phenobarbital (PB) administration leads to a decrease in simulated T_4 concentration and a compensatory increase in simulated TSH concentrations (not shown).



Compound	Process	IC50	Unit	Source
MMI	T4_synth	2.2	µmol/l	9
PTU	T4_synth	1.2	µmol/l	10
PTU	T3_synth	1.2	µmol/l	10
PTU	T4->T3	0.5	µmol/l	fitted

Figure 2. Developed QST model adequately captures effects of T_3 and T_4 synthesis/conversion inhibitors on thyroid hormone levels. (A) Dose dependent reduction in **T_3**, **T_4** levels and compensatory TSH increase in rats after MMI administration.[6] (B) **T_3**, **T_4** levels during treatment of hyperthyroid human patients with MMI.[7] (C) **T_3** and **T_4** levels in patients with Grave's diseases during switch from PTU to MMI treatment.[8]

Discussion

The QST model builds on earlier published models for thyroid hormone homeostasis [3-5]. The distinct features of the presented model include: a) physiologically based kinetics modelling of thyroid hormones and perturbators; b) focus on model validation with disruptors of the HPT axis to enable robust parameterization, current version of the model is based on more than 60 datasets extracted from the literature; c) parallel development of rat and human model parameterisations to enable interspecies comparison and application of the model in combination with the microphysiological systems.

Conclusion

The QST model adequately captures literature data for thyroid hormone baseline levels and kinetics as well as thyroid hormone changes in the presence of the HPT axis perturbators. The model enables the quantitative evaluation of changes in thyroid hormone levels induced by novel disruptors of the HPT axis based on known modes of action, in vitro potency data, and kinetic properties of TDCs. The availability of structurally compatible models for rat and human enables validation of model predictions for TDCs mediated changes in thyroid hormone levels in vivo with informed experimentation in rats.

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