National Centre for the Replacement Refinement & Reduction of Animals in Research

NC3Rs/POEMS Network Maths Study Group - Applying mathematics to 3Rs problems

Mathematical modelling to reduce animal use in neurodevelopmental safety assessment in humans.

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Background to the Problem

All environmental pollutants, pharmaceutical, crop protection and industrial chemicals go through a battery of tests, many of which involve animals, to assess their potential for inducing adverse effects in humans and the environment. A common finding during these investigations is the induction of Phase II xenobiotic metabolism in rats. This results in increased thyroid hormone metabolism.

Thyroid hormones are essential for the control of metabolism and development, especially nervous system development. Therefore there is a concern that altered thyroid hormone levels during critical periods of development would result in adverse outcomes in the developing foetus. This has led to calls from the regulatory agencies, e.g. the US Environmental Protection Agency (US EPA) to perform additional "developmental thyroid" studies in rats to assess the risk to the foetus and infants.

By using mathematical modelling can we determine whether, and under what conditions, we can confidently use the no-effect level of drugs and chemicals on thyroid hormones in male adult rats to be suitably protective for human health, and negate the need for additional animal studies?

Details of the problem

Thyroid hormone homeostasis is maintained through a negative feedback system involving the hypothalamus, pituitary and thyroid glands (HPT axis) as shown in Figure 1. In humans, the free concentration of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) are low because they are mostly bound to thyroxine-binding globulin, transthyretin or albumin. Rats do not have thyroxine-binding globulins and consequently free concentrations are higher, metabolism is faster and the thyroid system is more active than humans, making them less than ideal models for studying human thyroid hormone-dependent developmental toxicities.

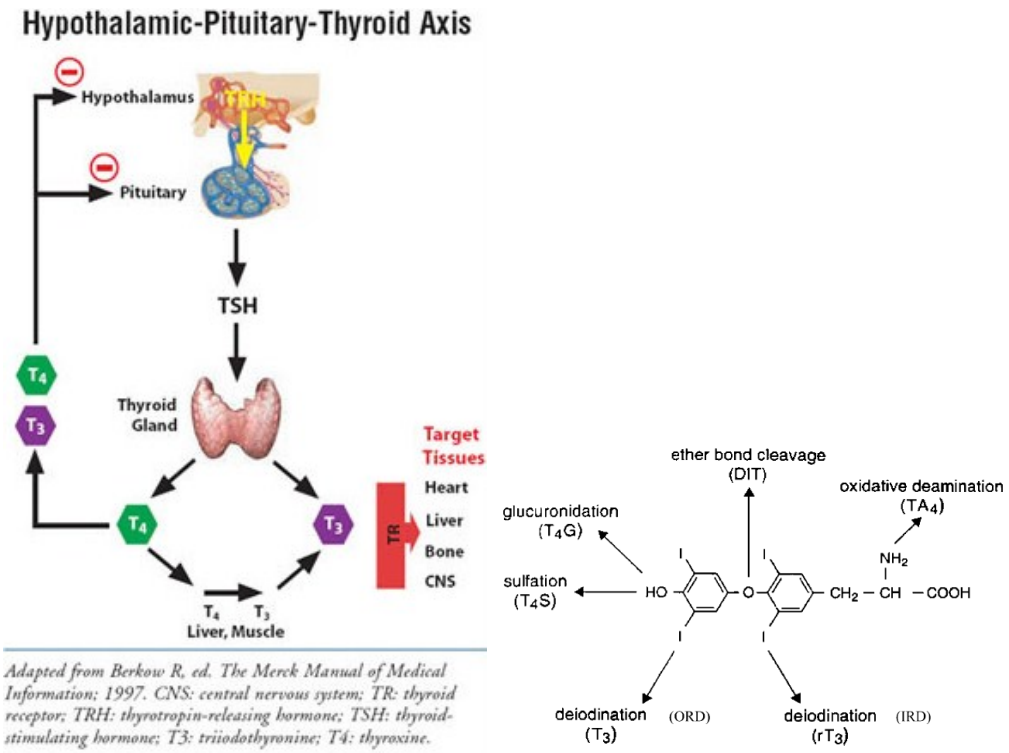

Figure 1: The hypothalamus, pituitary and thyroid glands (HPT axis) and its physiological interactions showing on the left the role of T3 and T4. The figure on the right shows the chemical structure of T3 and T4.

T4 and T3 can cross cell membranes, however they can also be transported across the blood-brain barrier, where T4 especially can act on the pituitary gland and hypothalamus to negatively regulate the production of thyroid stimulating hormone (TSH) and thyrotropin releasing hormone, respectively; hormones essential in the synthesis of T4 and T3. T3 and T4 can be metabolised to inactive forms and can also be conjugated by a number of uridine 5'-diphospho-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) to increase clearance from the liver into the bile (see Figure 1).

One of the most frequently observed effects in safety testing of chemicals is induction of xenobiotic metabolism systems in the liver. This adaptive response to a chemical permits the clearance of that chemical. However it also increases the expression of T3 and T4 UGTs. In the male rat this results in decreased T3/T4 levels, increased TSH, prolonged proliferative stimulation of the thyroid and benign tumours. These tumours are known not to be relevant for humans due to differences in response in the human HPT axis to decreased T3/4, compared to the rodent. Standard practice would be to demonstrate the perturbation of thyroid hormone levels using a variety of doses and establish a no-effect level dose where no perturbations in thyroid hormone levels are observed.

Human data show that maternal thyroid hormones are necessary for early foetal neurodevelopment and that normalisation of maternal thyroid T4 levels when in a hypothyroid state is required to prevent mental retardation in children. Once the foetal thyroid is able to produce thyroid hormones, there is a shift so that the maternal supply of thyroid hormones is quantitatively less important (see Figure 2).

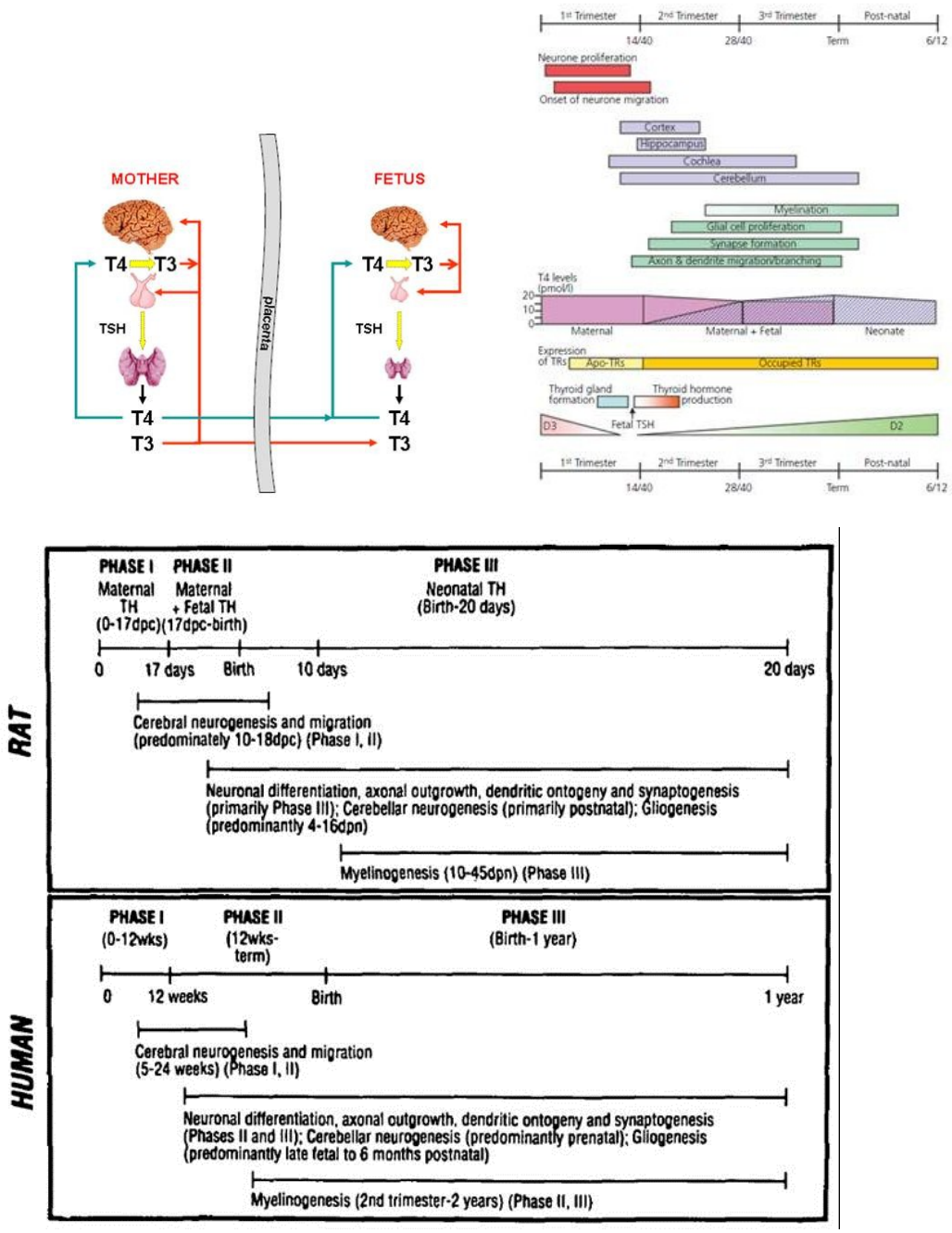

Figure 2: Brain neurological development relative to thyroid function in the rat and the human. TH, Thyroid hormones; dpc, days postconception; dpn, days postnatal.

To adequately assess the risk to human neurodevelopment caused by chemicals that induce UGT enzymes in the liver, a model will have to integrate many things (1) the double negative feedback system controlling thyroid hormone secretion, (2) kinetics and metabolism in two nested compartments (the mother and foetus in placenta), (3) extrapolate across sex (adult male to pregnant and lactating female), (4) extrapolate across changing expression of key components of the system at different life stages and (5) extrapolate across species from the data that is available.

Ideas and data for informing possible mathematical models

- Many models of the control of thyroid hormone homeostasis have been published, for review see [1], some of these may be a useful starting point. These models have focussed on supporting therapies and iodine deficiency, for example, but have not been integrated to explore the impact on the developing foetus. The current model would hope to achieve this.
- Published PB-PK models on perchlorate and iodine deficiency and thyroid hormone homeostasis. Also, there is associated literature on thyroid hormone levels in rat pups and dams, and humans after propylthiouracil (PTU) or perchlorate treatment or as a consequence of iodine deficiency.
- Published literature exists on the substrate specificity of the thyroid hormone deiodinases and UGT isoforms and their ontogeny during development of both rat and human foetus and liver/placenta [2].
- General understanding of similarities and differences in thyroid hormones during pregnancy in rats and humans [3,4].
- Data on the extent of thyroid hormone changes that cause adverse effects is known in human clinical data and in rodent studies.
- Data on UGT induction and size of effect on thyroid hormones in adult male rats is known.
- Similar data for some compounds in human clinical use is also known.

Questions you would like to see answered

1. Can you simulate the dose response of thyroid hormone alterations caused by T3/T4 metabolism induction during the developmental period sensitive to thyroid perturbation (foetal, neonatal and infancy)?
2. Can you extrapolate the thyroid hormone dose response in a male rat to the human foetus & neonate and identify if there is a potential for interaction with established risk factors for thyroid hormone perturbations such as iodine deficiency. Can you suggest refined study designs, data gaps and methods to permit extrapolation without having to conduct a developmental thyroid study in rats.

The potential impact on animal use

The design of developmental thyroid studies under the USEPA guideline would involve testing in the region of 1500 to 2000 rats per study (depending on litter size of the strain used). This estimate does not include any that might be required for a preliminary study to ensure appropriate dose level selection. If the modelling work can successfully show that male adult rat thyroid hormone perturbations caused by UGT induction can always be protective of human health, then the need to conduct these studies can be eliminated with the associated reduction in animal usage.

Relevance to medicine and healthcare

The proposed modelling work would extend existing thyroid models to cover key developmental stages when critical neurodevelopmental effects of thyroid hormones are occurring.

In many parts of the world hypothyroidism (whether through thyroid disease or iodine deficiency) contributes to childhood neurological impairments, understanding whether UGT induction caused by pharmaceuticals or trace environmental chemicals is able to exacerbate these effects has implications both for clinical practise and public health.

References

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