Thyroid hormone system disruption and adverse effects on the developing brain; recent scientific advancements in ATHENA and a regulatory way forward

Main author: Marta Axelstad (National Food Institute)

Co-authors: Marta Axelstad, Louise Ramhøj, Terje Svingen, Jermaine Ford, Mary Gilbert, Andreas Kortenkamp

INTRODUCTION

Adequate supplies of thyroid hormones (TH) are crucial for proper brain development. Exogenous substances that can disrupt the TH system, largely detected by alterations in TH in serum, raise concern for adverse effects on neurodevelopment. Current OECD Test Guidelines lack specific and sensitive methods to assess TH system-dependent neurodevelopmental impairments, owing largely to our limited understanding of the relationships between concentrations of TH in serum, target tissues, and the downstream effects on brain development. The European regulatory community has begun to address this issue through a variety of research efforts, including the Horizon 2020-funded EURION project; ATHENA.

METHODOLOGY

We are investigating novel readouts of developmental neurotoxicity (DNT) that are more specific to TH system disruption than the traditional assays of regulatory DNT guideline studies. In a series of developmental exposure studies in Sprague-Dawley rats, the effects of the drugs propylthiouracil (PTU) and methimazole (MMI) were compared with those induced by several environmentally relevant TH system disruptors, including DE-71 (a mixture of polybrominated diphenyl ethers), the UV-filter octyl-methoxycinnamate (OMC) and the pesticide amitrole. We assessed the formation of periventricular heterotopia, i.e. clusters of ectopic neurons in the white matter of the corpus callosum, transcript levels of TH-responsive genes in the neocortex, and TH concentrations in the serum and brain of developing offspring.

RESULTS

The studies have confirmed that developmental exposure to PTU and MMI causes formation of periventricular heterotopia in rat offspring. Exposure to both drugs also depressed TH-dependent gene transcription in the brain. Similar effects were seen after developmental exposure to the pesticide Amitrole, while the DE-71 mixture failed to affect these endpoints in the brain despite severe reductions in serum T4 concentrations. Brain hormone data are forthcoming.

DISCUSSION

The novel neurological endpoints examined here are clearly more specific towards TH disruption than traditional DNT endpoints, yet failed to reveal effects of certain TH system disruptors. By measuring TH concentrations in the brain, we are hoping to fill important knowledge gaps and improve our understanding of TH system disruption and the potential for DNT. However, the methods employed were not sensitive enough to detect neurotoxicity of all chemicals despite successfully detecting TH disruption. Therefore, in order to protect pregnant women and their foetuses from potentially harmful exposure to TH system-disrupting chemicals, regulatory decision-making must default to a reliance on serum T4 decreases alone until better test methods become available.