Thyroid hormone disrupting chemicals and their influence on the developing rat brain

The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are produced in the thyroid gland, and besides their role in the body's metabolic rate, they also play a determining role during foetal and neonatal brain development. Because thyroid hormones (TH) are needed for proper nerve cell differentiation and proliferation, normal status of these hormones during early development is crucial, and in humans even moderate and transient reductions in maternal T4 levels during pregnancy can adversely affect the child's neurological development. In order to maintain correct levels of THs, the body is dependent on sufficient iodine intake but several substances in the environment may also affect thyroid status. These are called thyroid disrupting chemicals (TDCs), and they are xenobiotics that can change the levels of circulating THs. The TDCs are made up of a wide range of chemical structures and include industrial chemicals, pesticides and ingredients used in personal care products. A way of getting more insight into the causal relationship between exposure to endocrine disrupters, their effects on TH levels and subsequent adverse effects on brain development, is by investigating it in animal studies. Therefore, the overall purpose of this Ph.D. project was to use an animal model to examine how neurological development is affected by pre- and postnatal exposure to TDCs, and to find out whether behavioural changes in the offspring could be predicted simply by measuring TH levels in the blood from exposed dams. This knowledge could enable regulatory authorities to easier identify the risks of developmental neurotoxicity after exposure to TDCs. The project included three developmental neurotoxicity studies in rats. In the first study, the known thyrotoxic drug propylthiouracil (PTU) was tested. This was done, in order to have a reference with regard to T4 reductions and behavioural outcomes in our laboratory. Hereafter two environmentally relevant chemicals were investigated. The first was the ultra violet (UV)-filter octyl methoxycinnamate (OMC), the other was the fungicide mancozeb. Both compounds are very widely used, and for both, studies have shown thyroid disruption to be a very sensitive endpoint but no developmental neurotoxicity studies have previously been published. The overall experimental design was as follows: time mated rat dams (n=15-20) were dosed with the test substance from gestation day 7 until the end of lactation at postnatal day (PND) 16, thereby exposing the offspring indirectly to the test substances via placental and milk transfer. One week after dosing had begun, blood samples from the dams were collected and analysed for serum T4 levels. On the last day of dosing some of the offspring were sacrificed, blood samples were collected and several organs were excised. From each litter a few offspring were weaned for further neurobehavioural assessment, which included tests of spatial learning and memory, motor activity levels and startle response. Hearing function was also assessed, along with additional reproductive toxicity endpoints. The results from the first study showed that developmental exposure to the known thyrotoxic compound PTU, caused hypothyroidism in both dams and offspring, and adversely affected the offspring’s brain development. Both dams and offspring had significantly decreased T4 levels during the dosing period, and their thyroid glands were severely affected. The expected neurobehavioural and auditory effects were seen, as learning and memory was impaired in the adult male offspring, while both males and female offspring showed hyperactivity and impaired auditory function. The observed changes in behaviour and hearing ability were significantly correlated to reductions in maternal T4 levels during gestation, indicating that these could be an indicator of the severity of behavioural and auditory defects later in life. In the OMC study, all tested doses markedly decreased T4 levels in dams, while the thyroid effects in the offspring were not very severe. OMC exposed male offspring showed reduced reproductive organ weights and decreased sperm counts in adulthood, effects that were probably mediated by OMC’s estrogentic properties. The offspring’s behaviour was also affected, however, differently than expected. In female offspring, motor activity levels were decreased in the highest dose group, while low and high dose males showed improved spatial learning abilities compared to controls. These behavioural changes were not correlated to maternal T4 levels, and were probably not mediated by early T4 deficiencies, as they differed substantially from effects seen in other studies of developmental hypothyroidism. In the mancozeb study, exposure of pregnant dams to the fungicide caused significant decreases in dam T4 levels during gestation. However, on PND 16 the thyroid system in the offspring was unaffected. Furthermore, no effects on reproductive endpoints and no behavioural changes were observed. The results from the three studies indicate that while PTU was readily transferred to the offspring, toxicokinetic factors may have affected placental and milk transfer of OMC and mancozeb, and thereby limited the offspring exposure. In the two latter studies, it was demonstrated that maternal T4 deficits during gestation were not correlated to behavioural outcome in the rat offspring, and unlike what is seen in humans, were therefore not good predictors for adverse neurobehavioural development. Based on these results, it was concluded in the thesis that in rats, measurements of prenatal T4 decreases alone cannot be used for regulatory purposes to predict developmental neurotoxicity, after exposure to chemicals that affect the TH system. A possible explanation for the observed differences between rodents and humans could be that while most of the brain maturation in humans happens prenatally, much happens postnatally in the rat. Prenatal T4 deficits may therefore be more critical for neurobehavioural development in humans than in rats. In conclusion, at present we know too little about the timing of TH deficiency, and of the complex array of feedback mechanisms and compensatory processes in the thyroid hormone system, to use maternal T4 measurements as predictors for adverse behavioural effects in offspring.

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