Impact of thyroid hormone disruptors during embryonic development

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INTRODUCTION

The rates of non-communicable diseases such as neurodegenerative disorders (Alzheimer's disease, multiple sclerosis) or neurodevelopmental disorders (attention deficit disorder and hyperactivity) have increased during the last 20 years. In addition, the rate of congenital hypothyroidism in France has also increased over the past 30 years. Recent data correlate fine variations of maternal TH during embryonic development with cognitive changes in children, detectable as early as the age of three (Bornehag et al., 2021; Korevaar et al., 2017). Daily exposure to dozens of chemical molecules that are potentially deleterious alone or in mixtures and which generate or amplify variations of TH levels during a critical developmental phase that represents embryo-foetal development is therefore particularly worrying.

METHODOLOGY

We previously showed in 2017 that 15 substances commonly measured in amniotic fluid disrupted the proper functioning of TH and impacted neural development (Fini et al., 2017). We investigated the effects of this mixture on brain and thyroid development and a number of its constituent molecules using relevant and complementary models.

RESULTS

- Using Xenopus embryos, exposed during the whole developmental phase when only maternal THs are available, we showed modifications of the brain transcriptome, and in particular a significant alteration of the expression of genetic coding for key actors of TH signalling (deiodinases, membrane transporters, nuclear receptors, etc.). Interestingly, signs of central hypothyroidism are visible before proper TH synthesis. We also evaluated the impact of the molecules on the swimming behaviour of the larvae and, in the longer term, on the neuron/glia ratio.
- We evaluated the impact of exposure to these products during the remyelination of optic nerve axons according to a previously established protocol (Mannioui et al.,

2017). We showed that the mixture and in particular certain chemical families significantly slow down the remyelination of axons.

- Using ex vivo cultures of murine neural stem cells in neurospheres, we were able to show that the mixture, when perfluorinated, impacts the proliferation into stem cells and their differentiation.

DISCUSSION

Overall, these results show that, during critical phases of embryonic development, chemical molecules present at low doses can have an impact at the cellular level on the proliferation of neural stem cells and the myelination of axons, and, at the tissue level, can affect the neuron/glia ratio and the establishment of the foetal thyroid and affect the behaviour of individuals. This highlights the advantage of using complementary strategies to investigate mechanisms and deleterious effects, but also the need to consider mixtures in experimental studies and regulatory risk assessments.