Developmental exposure to thyroid disruptors: misprogramming of the brain’s stem cells in later life?

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Introduction: Ever since the discovery of neural stem cells (NSCs) in the adult mammalian brain, scientists have been trying to decipher which signals govern their turnover and lineage commitment to generate neurons and glia. Understanding their role in nervous tissue homeostasis can provide new insights into the etiology of several neurological disorders, and might one day be turned to our advantage to promote endogenous brain injury repair. Others and we have identified thyroid hormone (TH) as a key factor transcriptionally regulating NSC behavior in the largest niche of the adult mammalian brain: the subventricular zone (SVZ).

TH is often considered a classic hormone, of which most is known with regard to its developmental and metabolic actions in vertebrates. However, two revolutions have revived the field. Next to the thyroid axis governing systemic TH homeostasis, tissue-specific TH regulation comprises a second level of control, including each cell type’s transcriptome independently of one another. Deiodinases, enzymes activating the ‘prohormone’ T4 into the biologically active T3, are critically involved in TH action. In parallel with this increase in TH availability of T3 able to bind the nuclear TH receptors, determining transcriptional activity. Second, research has revealed alarming connections between continuous, low-dose exposure to thyroid disrupting chemicals and abnormal human brain development. Epidemiological data have shown that even subclinical alterations in TH serum levels during pregnancy reduce the cortical grey matter volume in newborns, resulting in a population-level drop of a few IQ points (Korevaar et al., 2016). We hypothesized that TH coordinates postnatal SVZ reorganization at the transcriptome level, and that any disruption of TH action during this window could therefore misprogramme NSCs, altering the neuron-oligodendroglial output in adult life with implications for functions that depend on it.

Our recent findings: Using open access single-cell RNA-seq data from dissected murine SVZs, and by visualizing single mRNA transcripts with RNAScope, we found a global absence of TH-converting enzymes and-transporters in all SVZ cell types at postnatal day 2 (P2) (Vancamp et al., 2022). However, at P20, just after the peak in TH serum levels, Mct8, Oatp1c1, Dio2, Dio3, and Thra (encoding Tra2 and Tra1, the most prevalent TH receptor in the brain) were dominantly expressed in NSCs. Expression patterns of TH regulators have always been a strong indication for the intracellular T3 status as well as for what happens at the level of TH-target genes. In our study, they indicated that during and after the TH peak, the majority of NSCs possesses the machinery to autoregulate their intracellular TH concentration, allowing for TH action. In parallel with this increase in TH with inadequate TH levels during development bare an increased risk of generating irreversible structural abnormalities with functional repercussions in later life. Epidemiological data have shown that even subclinical alterations in TH serum levels during pregnancy reduce the cortical grey matter volume in newborns, resulting in a population-level drop of a few IQ points (Korevaar et al., 2016). We hypothesized that TH coordinates postnatal SVZ reorganization at the transcriptome level, and that any disruption of TH action during this window could therefore misprogramme NSCs, altering the neuron-oligodendroglial output in adult life with implications for functions that depend on it.

Perspectives for toxicological research: We identified the SVZ as a brain region vulnerable to developmental thyroid disruption. Of note, perturbation of one hormonal axis can bring the cross-talk with other hormonal pathways out of balance, potentially worsening the phenotype, knowing that SVZ development and function depend on other hormones as well. Hence, it should be additionally tested how chemical disruption of these endocrine pathways affects the above-mentioned processes. That knowledge can promote the SVZ to a region of interest to evaluate whether a chemical substance possesses neurotoxic properties or not, using our well-established read-outs.

Over the past years, a general picture emerged of how TH and the ensemble of cellular regulators influence the capacity of adult SVZ-NSCs to generate either new neuroblasts or oligodendrocyte precursor cells (OPCs) in mice. Gain- and loss-of-function experiments first showed that the T3-occupied receptor TRα1 in adult SVZ-progenitors repressed Sox2, a gatekeeper of NSC identity, and stimulated neuronal lineage commitment and neural progenitors cell migration (López-Juárez et al., 2012). Later in 2017, it was shown how the presence of the T3-activating Dio2 decreased MCT8 and OATP1C1, the resulting hormonal axis can bring the cross-talk with other endocrine hormones as well. Hence, it should be additionally tested how chemical disruption of these endocrine pathways affects the above-mentioned processes. That knowledge can promote the SVZ to a region of interest to evaluate whether a chemical substance possesses neurotoxic properties or not, using our well-established read-outs.

These observations in adult mice made us question whether TH could also affect the cellular SVZ organization during early life stages. The postnatal SVZ structurally reorganizes and embryonically generated NSCs reactivate to start generating neuroblasts and OPCs at a steady pace throughout adulthood. During this phase, which occurs over the first three weeks after birth in mice, TH serum levels gradually rise and peak at the beginning of the third postnatal week, suggesting TH could influence SVZ remodeling. TH exerts an orchestrated role in other developing brain regions as well, such as the cortex, the cerebellum, and another stem cell niche: the subgranular zone of the dentate gyrus. Interestingly, in contrast with hypothryoid insults to the adult brain that are usually reversible, periods of inadequate TH levels during development bare an increased risk of generating irreversible structural abnormalities with functional repercussions in later life. Epidemiological data have shown that even subclinical alterations in TH serum levels during pregnancy reduce the cortical grey matter volume in newborns, resulting in a population-level drop of a few IQ points (Korevaar et al., 2016). We hypothesized that TH coordinates postnatal SVZ reorganization at the transcriptome level, and that any disruption of TH action during this window could therefore misprogramme NSCs, altering the neuron-oligodendroglial output in adult life with implications for functions that depend on it.

Figure 1 | Overview of the major events in murine SVZ development and the role of thyroid hormones therein. While the SVZ-NSCs are generated during embryonic development, they postnatally reorganize under the influence of genes and extracellular factors. We found that when postnatal TH serum levels peak, intracellular TH action in NSCs increases, coinciding with the onset of SVZ-neurogenesis. Consequently, this window represents a phase where SVZ-NSCs are particularly vulnerable to chemical disruption. Indeed, developmental exposure to the TH-synthesis blocker PTU dysregulated TH-target genes, and permanently disrupted the neuron/oligodendroglial output in the SVZ. As a consequence, young adult mice developmentally exposed but fed a normal diet thereafter, underperformed on olfactive behavior tests that normally depend on proper SVZ-neurogenesis. Scale bar: 50 µm. E: Embryonic day; EDC: environmental toxicant; TRα1: thyroid hormone receptor alpha 1; TH: thyroid hormone. Data source: Vancamp et al. (2022) combined with unpublished figures from the authors.

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To understand and recognize the effects of thyroid disruptors on neurodevelopment, one study already assessed the developmental exposure of decabromodiphenyl ether (BDE-209) using a mouse model. This research indicates that thyroid disruptors can cause abnormalities in the murine subventricular zone. Stem Cell Reports 17:1-7 (2021).

Future challenges: To understand and recognize the effects of real-life chemical exposure, we need comprehensive data on thyroid hormone signaling in the brain to fully understand how thyroid disruptors affect early neurodevelopment. We must develop new tools to measure and detect thyroid disruptors, as well as increase our understanding of how exposure to these chemicals affects brain development.

We hope that our study has provided the next step in this challenging quest, by offering fundamental knowledge on how and when thyroid normally acts on the SVZ, as well as providing a framework for future studies. Additionally, our findings highlight the importance of identifying the chemical compounds that may affect thyroid hormone signaling in the brain, and how these disruptors could affect other organs.

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- Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.
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- Additional file: Additional Figure 1: Proposed chain of events in the mouse SVZ and related behaviors following developmental exposure to thyroid disrupting compound(s).

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Additional Figure 1 Proposed chain of events in the mouse SVZ and related behaviors following developmental exposure to thyroid disrupting compound(s).

Further information regarding the proposed questions as well as confirmation of the causal relationship between these events will allow constructing an adverse outcome pathway that can be used as a standard assay in toxicological studies. The questions at the right give an idea of the complexity that toxicological research has to deal with in order to grasp the exact mode of action of an endocrine disruptor, and what consequences it can have for an organism. NSC: Neural stem cell; SVZ: subventricular zone; TH: thyroid hormone.