Prix de la SNE Building a brain: The need for thyroid hormone and protein during foetal development

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Thyroid hormone (TH) is a multifaceted hormone, promoting neurodevelopment, metabolism and mental wellbeing. The discovery of the TH transporter MCT8, whose mutations were linked to a rare psychomotor disability syndrome, raised questions on how its functional absence contributes to the physiopathology of these patients. In Leuven, Belgium, we used the chicken embryo to knock down MCT8 and reduce TH action in specific neural stem cell (NSC) populations that give rise to key cell types such as the Purkinje cells and GABAergic cells, and observed cell cycle perturbations, hampered migration and impaired differentiation.

At the Natural History Museum in Paris, we then investigated how TH and disruptors of TH action affected NSCs of the mouse brain. We found how exposure to the endocrine disruptor Bisphenol F interfered with gene expression and adult neurogenesis, resulting in altered olfactory behaviour. In another study, we revealed that exposure to the TH disruptor pyriproxyfen worsened outcomes of ZIKA virus infection in NSCs, identifying a potential mode of action explaining why more cases of microcephaly were diagnosed in North-Eastern Brazil regions. Lastly, we found that the capacity of adult NSCs to differentiate into neurons and oligodendrocytes, the latter responsible for generating myelin, had changed due to impaired TH action during development. Building forth on these data in Germany, we applied proteomics together with conditional knockout mouse models, and identified the striatal enzyme PDE10A as a novel target underlying locomotor problems in patients.

At the PhAN unit of the INRAE in Nantes, we are currently investigating how protein restriction (PR) interferes with early brain development, more specifically the hypothalamus, the neuroendocrine control centre of an organism's metabolism. We thereby focus on hypothalamic neurogenesis in rats at gestational day 15 (G15), and at G17 when neuronal differentiation takes place. We feed dams an 8% isocaloric PR diet for four weeks prior to mating, followed by a 4% PR diet until either of both time points. The control group receives a diet containing 20% of proteins. Preliminary data have shown that both foetus and placenta are negatively impacted by the diet, and that hypothalamic cell proliferation is impaired. We plan to perform single-cell RNA-Seq on cultured cells grown from dissected hypothalami at G15 to identify which cell types are the most vulnerable to perinatal PR, and which associated molecular pathways are dysregulated. These data ultimately offer insights into the origins of metabolic disease in adult life.