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Expression and Function of Thyroid Hormone Receptor Alpha 1 in the Brain

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ABSTRACT

Thyroid hormone is fundamentally important for development and maintenance of adult brain functions and maternal hypothyroxinemia during pregnancy can lead to a severe mental retardation known as endemic cretinism. The first realization that endemic cretinism is caused by iodine deficiency and its association with thyroid hormone was made a century ago; this eventually resulted in dietary supplementation programmes, e.g. iodination of table salt. Moreover, routine screening of newborns and subsequent treatment prevents the irreversible psychomotor defects caused by congenital hypothyroidism. However, the understanding of the mechanism for how thyroid hormone exerts its effects during brain development is limited. In addition, the fetal consequences of maternal hypothyroxinemia in the absence of iodine deficiency are not generally accepted.

The aim of the work in this thesis was to elucidate functions of thyroid hormone in the developing nervous system. For this we studied the cellular mediators of thyroid hormone action, i.e. nuclear thyroid hormone receptors (TRs). Recent publications suggested that many of the consequences of hypothyroidism in the brain are caused by the repressor activity of the unliganded isoform TRα1. We therefore generated mice in which a mutant TRα1, with lower affinity to ligand, confers a "receptor-mediated hypothyroidism". In **paper I** we show that these mice have locomotor aberrancies that bear a striking resemblance to that seen in endemic cretinism. Indeed, we could show that the defects were founded during pregnancy and that the offspring was dependent on maternal thyroid hormone for proper motor functions in the adult. Furthermore, we identified that specifically the parvalbumin subtype of GABAergic interneurons in the cortex showed a delayed development, correlating with the locomotor phenotype. This was accompanied by an impaired neuronal network activity and a lowered number of fast-spiking interneurons. In **paper II** we investigated if the reduced inhibition resulted in lowered seizure susceptibility. Surprisingly, the mutant mice were partially resistant to seizures induced by the $GABA_A$ receptor antagonist pentylenetetrazol, a result that was mirrored in hippocampal slice preparations *in vitro*. Moreover, patch clamp recordings revealed that the pyramidal cells of the mutant mice were hypoexcitable.

Although the TRs were cloned over 20 years ago their expression in specific cell types in the brain was still unknown due to a lack of reliable antibodies against them. We therefore decided to generate mice that express a chimeric TRα1-GFP protein from the *Thra* locus. The results in **papers III** and **IV** showed that TRα1-GFP was first expressed in postmitotic neurons of the embryonic telencephalon, the postnatal cerebellum and in the adult hippocampal neurogenic niche. In the adult, essentially all mature neurons expressed TRα1, the exception being Purkinje cells in the adult. Expression in glia was limited to tanycytes lining the third ventricle and to the cerebellum. The effect of the unliganded TRα1 on adult neurogenesis was explored in **paper IV.** Here we could demonstrate that the aporeceptor activity of TRα1 caused a reduction in survival of postmitotic neuroblasts during adult-onset hypothyroidism.

We have made significant advancement towards understanding the damage resulting from endemic cretinism by identification of cells that develop improperly as a result of insufficient supply of fetal thyroid hormone and establishing that TRα1 expression is first turned on during later stages of neuronal maturation.

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