Thyroid hormone signaling in neurodevelopment: critical roles in auditory and visual sensory systems

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To identify functions regulated by thyroid hormone signaling in the nervous system, we have investigated mice lacking individual thyroid hormone receptor (TR) isoforms encoded by the *Thra* and *Thrb* genes. These studies show that TRs are unexpectedly critical regulators of hearing and colour vision. In the retina, the TRβ2 isoform regulates the diversification of cone photoreceptor subtypes required for colour vision. In the auditory system, TRβ is essential for hearing and controls postnatal cochlear maturation. Moreover, TRα1 and TRβ synergistically control a range of functions in hearing, as is evident from the exacerbated auditory defects in mice lacking all TRs. Thus, TRβ and TRα1 coordinate a set of late differentiation events at a critical time around the onset of hearing.

While TRs are a prerequisite for thyroid hormone signaling, it is likely that other factors modify TR activity at key developmental stages. Thyroid hormone may be metabolically activated or inactivated by deiodinase enzymes. In the early postnatal mouse cochlea, we identified prominent expression of type 2 deiodinase (D2) which converts thyroxine (T4) the main form of thyroid hormone in the circulation into T3, the major ligand of the TR. D2-deficient mice display deafness and a cochlear phenotype like that of TRβ-deficient mice. The findings suggest that D2 controls TR activation in the cochlea by locally amplifying T3 levels and that this enzyme confers upon the cochlea the ability to stimulate its own hormonal response at the appropriate time. Thus, an interplay between TRβ and TRα1 receptors and deiodinase hormone-modifying enzymes is likely to determine the cellular specificity and the timing of the differentiation events required for correct sensory development.

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Session 12