NEUROLOGICAL DISORDERS

Thyroid hormone receptors and neuronal dysfunction

Thyroid hormone receptor α1 (TRα1) has been implicated in the neurological complications of hypothyroidism, but its exact role in neuronal development and adult brain function has not been clear. Now, Venero and colleagues have shed light on the role of unliganded TRα1 in causing anxiety, memory deficits and motor dysfunction.

In vertebrates, the binding of thyroid hormone to TRα and TRβ triggers many cellular reactions. But when the natural ligand, triiodothyronine (T3), is limiting, for example, in hypothyroidism, TRs form complexes with other proteins such as co-repressors, an interaction that suppresses basal level transcription of target genes that are normally induced by ligand-bound TRs. The apo-forms of TRs are implicated in the abnormal development of the brain during hypothyroidism, which leads to irreversible motor dysfunction and reduced mental capabilities.

The TRα1 receptor accounts for 70–80% of TRs in neuronal tissues and is thought to be the most relevant in the development of the central nervous system. Venero *et al.* showed that knock-in mice carrying a mutated form of TRα1 (R384C), with a tenfold reduction in affinity for T3, had neurological abnormalities that presented at two stages of brain development.

At 12–14 weeks, TRα1 mutant mice were more anxious and less likely to explore new objects compared with wild-type mice. In the elevated plus maze, knock-in male mice froze more and reared less — both behavioural characteristics of anxiety — than wild-type mice. In addition, TRα1 mutant mice were not as inquisitive about an unfamiliar object as wild-type mice, and showed lower memory recognition for objects that they had already encountered. Although administration of high levels of T3 alleviated the anxious behaviour and restored the exploratory preference of adult mutant mice, symptoms only improved in adults, not juveniles (postnatal days 10–35), which suggests a neurophysiological role for TRα1 in adults.

The authors went on to investigate the effect of TRα1 on locomotor activity. After training on the Rotarod, mice carrying the TRα1 mutation stayed on the rod for shorter periods of time than wild-type mice. Interestingly, although T3 treatment of adult TRα1 mutant mice had no effect on their performance, treatment of juvenile mice (postnatal days 10–35) completely normalized the locomotor activity of adult mutant mice, which suggests that Trα1 has a role in brain development.

In humans, mutations of the *TRβ* gene result in the syndrome of peripheral resistance to thyroid hormones, but no mutations of TRα1 have been described. The results reported by Venero and co-workers suggest a clinical phenotype of anxiety and locomotor dysfunction without alterations in circulating levels of thyroid hormones. Moreover, these dysfunctions were ameliorated in TRα1 mutant mice by high levels of T3, which suggests that these neurological abnormalities could be circumvented by hormone treatment at the appropriate time.

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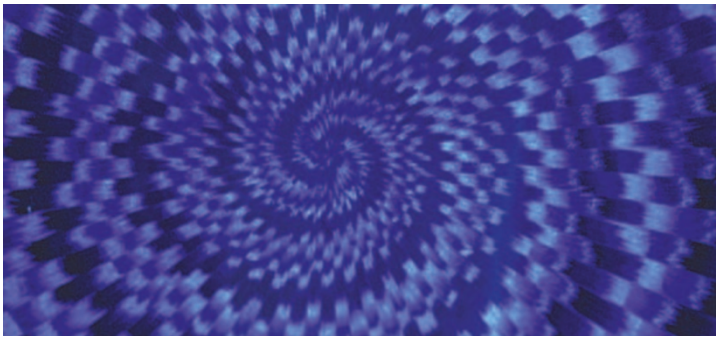
References and links

ORIGINAL RESEARCH PAPER Venero, C. *et al.* Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor α1 can be ameliorated by T3 treatment. *Genes Dev.* **19**, 2152–2163 (2005)



DEVELOPMENT

Top-Notch patterning

A new study by Mason and colleagues, published in *Development*, provides strong evidence that Notch activity is crucial for neurogenesis in the basal forebrain — specifically for the generation of striatal neurons from progenitor cells in the ventricular zone.

The striatum is segregated into two distinct compartments — patches (or striosomes) and the surrounding extrastriosomal matrix — each with specific biochemical and functional profiles. During development, patch neurons generally emerge ahead of matrix neurons, although the developmental events that guide the generation of neurons in these two compartments has, until now, remained unclear.

Both *Notch1* and *Notch3* are expressed in progenitor cells in the forebrain, and gain-of-function studies have implicated Notch signalling in the regulation of cell fate during forebrain development. However, because mutants that lack *Notch1* die before the onset of neurogenesis, it has been impossible to definitively establish the effects of Notch activity in neurogenesis or later stages of neuronal development.

To tackle this problem, Mason and co-workers used the Cre/*lox*P recombination system to create mice in which either *Notch1* or *Notch3* was selectively deleted and mice in which both *Notch1* and *Notch3* were eliminated. The absence of *Notch1* in the telencephalon from before the onset of neurogenesis selectively impaired the development of patch neurons, whereas matrix formation remained intact.

Although a lack of *Notch3* alone did not affect patch or matrix development, mice that were deficient in both *Notch1* and *Notch3* had a severe reduction in the number of matrix neurons. The authors therefore concluded that *Notch3* functionally compensated for the absence of *Notch1* in the single-knockout mutant mice to enable normal development of matrix neurons. In the double-knockout mutants, patch formation was further compromised, which indicates that *Notch3* activity also influenced patch development to a limited extent in the absence of *Notch1*. However, as patch development was also impaired in the single-knockout mice, it seems that *Notch3* could not functionally replace *Notch1*.

Importantly, in mice in which either *Notch1* or *Notch3* were deleted following progenitor cell migration from the ventricular zone in the telencephalon, development of both patch and matrix compartments in the striatum was unaffected.

These results indicate that Notch activity in progenitor cells in the ventricular zone is crucial for regulating the developmental timing that controls the generation of the distinct striatal compartments. By contrast, subsequent migration and differentiation of striatal neurons seem to proceed normally without the need for Notch activity.

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References and links

ORIGINAL RESEARCH PAPER Mason, H. A. *et al.* Notch signaling coordinates the patterning of striatal compartments. *Development* **132**, 4247–4258 (2005)