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microRNAs regulate puberty timing

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The onset of puberty is tightly regulated by neurons in the hypothalamus; disruption of this pathway can result in disorders such as hypogonadism and sterility. New findings, published in *Nature Neuroscience*, indicate that a microRNA (miR)-dependent mechanism regulates gonadotropin-releasing hormone (GnRH) production to control puberty timing.

"A postnatal increase in GnRH expression is essential for sexual maturation, but the molecular mechanisms controlling this increase and its timing have remained a mystery," explains Vincent Prevot, who led the study. Using mice with a GnRH neuron-specific knockout for the miR maturation factor Dicer, the team identified two miRs that control GnRH production during postnatal days P7–P12, shortly before puberty.

GnRH neurons lacking *Dicer* had significantly reduced levels of *Gnrh* itself and other transcripts known to activate its expression. Expression of *Cebpb,* which mediates nitric oxide-dependent repression of *Gnrh* expression, was also increased.

An *in silico* approach revealed potential miR binding sites in the promoters of genes that modulate GnRH production. The team then identified members of the miR-200 family (miR-200a and miR-429) that are differentially expressed between days P7 and P12 and enriched in GnRH neurons at P12. miR-200 is known to silence the transcriptional repressor *Zeb1*. All of the *Gnrh* transcriptional activators the team analysed had Zeb1 binding sites and, by injecting target site blockers (TSBs) for miR-200 into the preoptic area of the brain, the team saw increased *Zeb1* expression, which coincided with decreased expression of genes that normally activate *Gnrh*.

The investigators also identified miR-155, which down-regulates *Cebpb* expression, as being increased between P7 and P12. Importantly, blocking nitric oxide production rescued *Gnrh* expression in the *Dicer*-deficient mice.

Finally, the investigators used TSBs against miR-200 and miR-155 to understand their functional role. Mice injected with the TSBs underwent early onset of puberty (up to 10 days early in the miR-200 TSB mice), and adult mice had longer oestrous cycles than controls.

"These networks that sustain the postnatal increase in GnRH expression also appear to be at work during adulthood, as the blockade of miR-200/429/*Zeb1* binding in the hypothalamus affects oestrous cyclicity in adult female mice," clarifies Prevot. "Our data raise the intriguing possibility that miR-dependent epigenetic regulation of GnRH secretion could underlie the pathophysiology of human congenital hypogonadotropic hypogonadism when no mutations are found."

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ORIGINAL ARTICLE Messina, A. *et al.* A microRNA switch regulates the rise in hypothalamic GnRH production before puberty. *Nat. Neurocsci.* http://dx.doi.org/10.1038/nn.4298 (2016)