NEURODEVELOPMENTAL DISORDERS

Hormone therapy for Down syndrome

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Patients with Down syndrome (DS) show a wide array of symptoms, including infertility, loss of smell with age, and cognitive decline. Although support and educational programs can help to improve cognitive skills in patients with DS, there is no cure for the condition. A new study in *Science* suggests that gonadotropin-releasing hormone (GnRH) — a fundamental hormone for reproduction — is a promising treatment for cognitive deficits in DS.

GnRH is secreted in a pulsatile fashion by specialized neurons in the hypothalamus; the hormone controls reproduction by activating the hypothalamic-pituitary-gonadal (HPG) axis, which regulates the secretion of steroid hormones. Some GnRH neurons also connect to the cortex and hippocampus, brain regions that are associated with learning and memory. This observation prompted a team of researchers to explore whether alterations in the GnRH system might contribute to cognitive decline in patients with DS, particularly after puberty.

For their study, the investigators used a mouse model of DS (Ts65Dn mice) that overexpresses the mouse genomic region orthologous to human chromosome 21 and recapitulates key characteristics of human DS. First, they further characterized the mouse model, which revealed that Ts65Dn mice exhibit declines in olfactory and cognitive function after puberty, accompanied with a progressive loss of GnRH neurons and projections.

Next, the team demonstrated that the decrease in GnRH expression in adult mice was accompanied by a dysregulation of a network of several microRNAs, including miR-200b, which control GnRH expression in the hypothalamus. Adeno-associated virus (AAV)-mediated overexpression of miR-200b in the hypothalamus of Ts65Dn mice reversed alterations in gene expression associated with DS and rectified hippocampal synaptic transmission. Using several techniques to boost GnRH expression in Ts65Dn mice, including injections of cells and brain tissue grafts from healthy mice in the brain, chemogenetics and implantation of a minipump for pulsative delivery of native GnRH, the team was able to reverse olfactory and cognitive deficits in DS mice, demonstrating the critical role of GnRH in olfaction and cognition.

Finally, the researchers performed a pilot study in which they injected the hormone in seven male patients with DS. GnRH therapy improved cognition and brain connectivity in these patients, raising hope that the hormone could be used to improve the quality of life of patients with DS.

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