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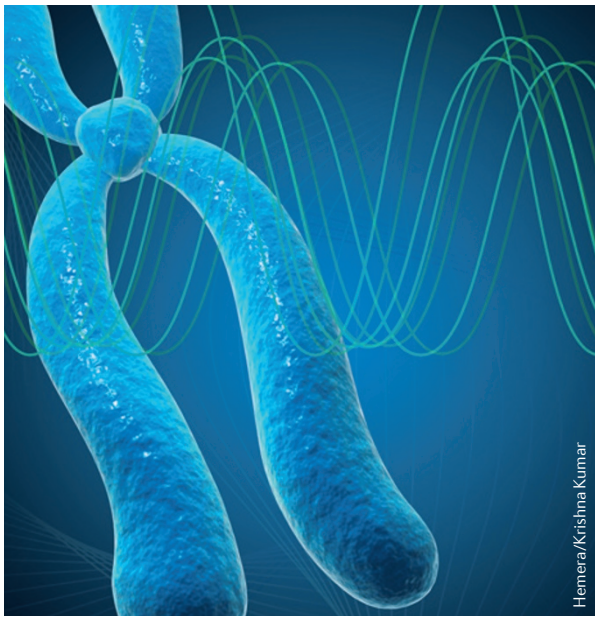
NEURODEVELOPMENTAL DISORDERS

Righting Rett syndrome with IGF1

> *Mecp2*$^{-/y}$ mice that were treated with both clenbuterol and rhIGF1 lived … 1.9-fold longer than vehicle-treated controls

Rett syndrome is a severe neurodevelopmental disorder that usually results from mutations in the gene that encodes methyl-CpG-binding protein 2 (MECP2). As MECP2 has many complex and diverse roles in the brain, the pathogenic mechanisms of Rett syndrome are not clear, and currently only symptomatic treatments are available. Now, two papers show that treatment with insulin-like growth factor 1 (IGF1) and/or the β_2-adrenergic receptor agonist clenbuterol can alleviate symptoms in MECP2-deficient mouse models of Rett syndrome. Moreover, these studies shed light on some of the mechanisms that underlie this devastating disease.

In a previous study, a tripeptide fragment of IGF1 was shown to alleviate some symptoms of MECP2 deficiency in mice — including abnormal breathing patterns, impaired motor coordination and cognitive deficits — but full-length IGF1 was not tested. Here, Castro *et al.* showed that male MECP2-null mice (*Mecp2*$^{-/y}$ mice) had lower serum levels of IGF1 than wild-type controls. As Rett syndrome usually occurs in heterozygous females, Castro *et al.* tested the effects of 3 weeks of daily injections of recombinant human IGF1 (rhIGF1) on symptomatic older (>6 months) female mice that were heterozygous for mutated *Mecp2* (*Mecp2*$^{-/+}$ mice). These mice showed improved breathing patterns and performed better in spatial-recognition behavioural tests than vehicle-treated *Mecp2*$^{-/+}$ animals, indicating that low levels of IGF1 may contribute to some symptoms of Rett syndrome. Moreover, rhIGF1 prevented abnormal monocular-deprivation-induced cortical plasticity in older *Mecp2*$^{-/+}$ mice, which suggests that IGF1 is needed for normal cortical maturation.



Hemera/Krishna Kumar

Rett syndrome often presents with abnormalities in adrenergic signalling, so adrenergic receptor agonism has been suggested to be a possible strategy to treat the disease. In a related study, Mellios *et al.* found that, compared with vehicle-treated controls, clenbuterol-treated female *Mecp2*$^{-/+}$ mice exhibited fewer apnoeas, more regular breathing and improved object-recognition memory, as well as better motor coordination on a rotarod test.

Interestingly, clenbuterol-treated *Mecp2*$^{-/+}$ animals had higher serum levels of IGF1 than did vehicle-treated *Mecp2*$^{-/+}$ controls. To investigate how β_2-adrenergic receptor agonism elicited these effects, the authors measured the cerebellar levels of brain-derived neurotrophic factor (BDNF), the transcription of which is regulated by MECP2. Compared with vehicle-treated *Mecp2*$^{-/y}$ animals, BDNF was upregulated in clenbuterol-treated *Mecp2*$^{-/y}$ mice and vehicle-treated wild-type mice.

A previous study showed that BDNF regulates the microRNA-processing factor lin-28 homologue A (LIN28A). In the current study, Mellios *et al.* found that, in *Mecp2*$^{-/y}$ mice, treatment with clenbuterol restored the cerebellar levels of LIN28A to wild-type levels. Using a hepatocyte cell line, the authors demonstrated that LIN28A is required for the normal production of IGF1. LIN28A is known to inhibit let-7 microRNAs, of which one (let-7f) can in turn inhibit *IGF1* mRNA; thus, these findings indicate that clenbuterol may increase levels of IGF1 in the brain via its actions on a microRNA-regulated pathway.

Finally, *Mecp2*$^{-/y}$ mice that were treated with both clenbuterol and rhIGF1 lived longer than controls that were given monotherapy and 1.9-fold longer than vehicle-treated controls. In humans, the chronic use of clenbuterol leads to serious side effects, so the authors caution against the use of β_2-adrenergic receptor agonists with poor therapeutic indexes. However, rhIGF1 is currently being tested in Phase II clinical trials in girls with Rett syndrome.

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ORIGINAL RESEARCH PAPERS Castro, J. *et al.* Functional recovery with recombinant human IGF1 treatment in a mouse model of Rett syndrome. *Proc. Natl Acad. Sci. USA* **111**, 9941–9946 (2014) | Mellios, N. *et al.* β2-adrenergic receptor agonist ameliorates phenotypes and corrects microRNA-mediated IGF1 deficits in a mouse model of Rett syndrome. *Proc. Natl Acad. Sci. USA* **111**, 9947–9952 (2014)