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Study suggests possible treatment for neurological disorder Rett syndrome

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Using injections of a small derivate of the protein insulin-like growth factor-1 (IGF-1), scientists at Whitehead Institute for Biomedical Research and MIT's Picower Institute for Learning and Memory have successfully treated a mouse model of the devastating neurological disorder Rett syndrome.

Rett syndrome is an inherited disease affecting one of 10,000 girls born. Infants with the disease appear to develop normally for their first six to 18 months, at which point their movement and language skills begin to deteriorate. Loss of speech, reduced head size, breathing and heart rhythm irregularities, and autistic-like symptoms are common by age four. Some symptoms may be mediated with prescription drugs, but no cure or truly effective treatment for the disease exists.

In a study appearing in the February issue of the *Proceedings of the National Academies of Sciences*, researchers showed that daily injections of an active fragment of IGF-1 in mice that expressed Rett-syndrome like symptoms could significantly reduce movement and respiratory irregularities. Although treated mice were not cured, the outcome is reason for optimism.

"This is the first realistic way for a drug-like molecule injected into the bloodstream to relieve Rett syndrome symptoms," says Whitehead Member Rudolf Jaenisch, whose lab collaborated with the lab of MIT and Picower scientist Mriganka Sur in the research.

In approximately 85% of girls with Rett syndrome, the disease is caused by loss of function of the MeCP2 gene, which is highly expressed during nerve cell maturation. Lack of MeCP2 expression impedes nerve cell growth, keeping the cells from forming projections, called spines, which are used for nerve-cell-to-nerve-cell communication. Recent genetic studies have shown that in mice with blocked MeCP2 expression, turning MeCP2 back "on" nudges the mice towards normal movement and lifespan—an indication that the disease could be reversible.

Although researchers have known which gene causes the vast majority of Rett syndrome cases, they have until now been unable to promote nerve cell maturation through administration of a drug, protein, or small molecule.

While researchers in Sur's lab had discovered that increased brain levels of IGF-1 promoted maturation of synapses, the connections between nerve cells that are the basis for brain functions, Emanuela Giacometti, a graduate student in Jaenisch's laboratory, was theorizing that IGF-1 might also increase the nerve cell spines in the lab's mouse model of Rett syndrome. Such mice lack the MeCP2 gene and at four to six weeks display symptoms quite similar to those in girls with Rett Syndrome, including difficulty walking, lethargy, and breathing and heart rhythm irregularities.

In a collaboration with the Sur lab to test how IGF-1 might affect these mice, Giacometti administered to two-week-old Rett mice daily injections of IGF-1 fragment. At six weeks, treated mice were significantly more active, had more regular breathing, and had more normal, regular heart rhythms than did untreated mice. In addition, the brains of treated mice were heavier and showed more nerve cell spines.

"Although the treated mice get better and their symptoms don't progress as fast as they normally would, the treated mice still get the symptoms.

So it's definitely not a cure, but it could be a co-therapy," Giacometti says.

Sur is also excited by the prospect of finding a drug treatment for Rett syndrome and other forms of autism. IGF1 is approved by the US Food and Drug Administration (FDA) to treat severe IGF-1 deficiency. "This represents a way forward towards clinical trials and a mechanism-based treatment for Rett Syndrome. We very much hope our research can offer some help for the patients who have this terrible disorder."

More information: Partial reversal of Rett syndrome-like symptoms in MeCP2 mutant mice, *Proceedings of the National Academy of Sciences*, February 9, 2009