

Nature's origami: protein folding mistakes and diseases

What is a protein?

[Proteins](#) are long strings of amino acids organized by folding into functional structures. In “conformational” diseases, gene mutations cause these proteins to be folded incorrectly. Just as a mis-folding of origami paper can make the difference between a beautiful crane and an unrecognizable wad of paper, so a mis-folding of a protein can be the difference between health and disease.



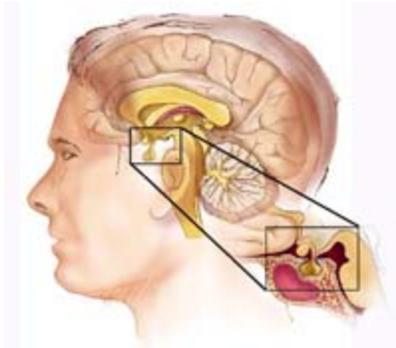
Levels of protein organization (left)	
1	Sequence of amino acids
2	Amino acids linked to hydrogen bonds
3	Amino acids folded
4	A protein consisting of more than one amino acid chain

What is a receptor?

A receptor may be thought of as a lock that allows an outside ligand or key to activate a response inside the cell. Located on the cell membrane or surface, a receptor is made up of a string of precisely folded [amino acids](#).



A team of Center scientists has discovered that the cause of a rare form of male infertility is a mis-folding of a protein that functions as a receptor in the pituitary gland at the base of the brain.

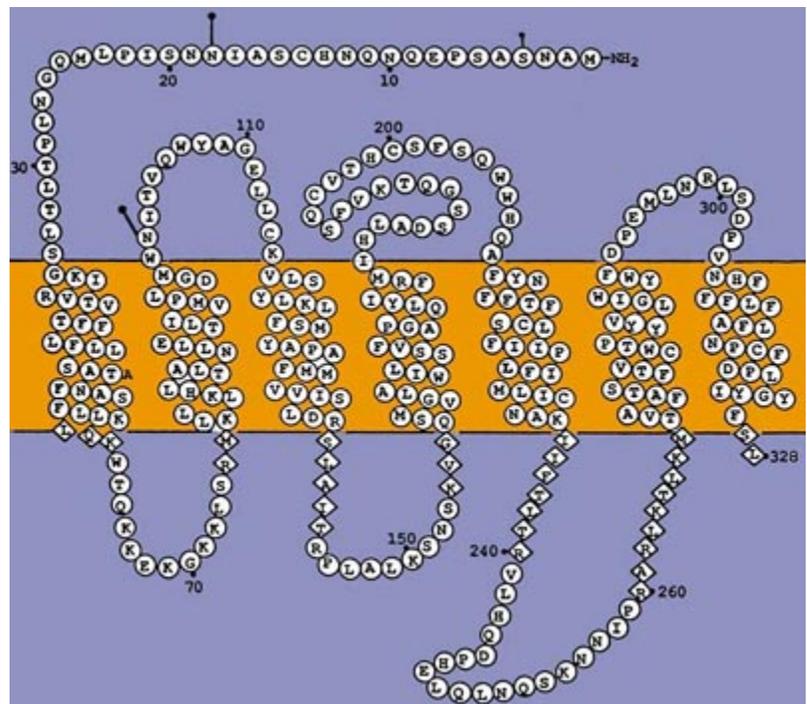


What is the pituitary gland?

The [pituitary gland](#), which is attached to the base of the brain, secretes hormones that travel in the circulatory system and, after reaching the gonads—ovaries and testes—govern several reproductive functions such as the onset of puberty, maturation of sperm and eggs, and sexual function.

The receptor in certain pituitary cells that binds GnRH is made up of a long string of 328 amino acids that cross the membrane seven times.

Even slight defects in the folding of the GnRH receptor may send a molecule to the wrong place in the cell where the ligand can't reach it — in effect, a lock hidden beyond the reach of its key.

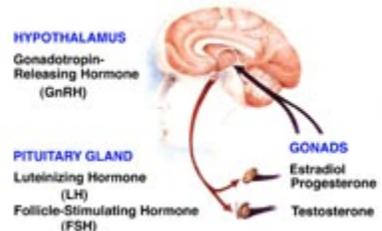


What is GnRH?

GnRH is the acronym for a brain hormone called gonadotropin releasing hormone. In normal, healthy people, GnRH binds to certain cells in the pituitary gland, stimulating them to release [hormones that, in turn, regulate the ovary and/or testis](#).

What is Hypogonadotropic hypogonadism?

[Hypogonadotropic hypogonadism \(HH\)](#) is a disease that interferes with reproduction. The interference comes about because GnRH cells in the pituitary fail to be stimulated—for the reason discovered by the ONPRC scientists: their receptors for GnRH have been misfolded and are thus beyond reach. Consequently, the pituitary hormones [FSH \(follicle stimulating hormone\)](#) and [LH \(luteinizing hormone\)](#) necessary for reproductive functioning are absent from the male testis or ovary.



“In the case of HH,” say the researchers, “the parts (in the pituitary cells) are good, but they are just in the wrong place.”

The ONPRC group has learned how to cure HH through a drug that induces the mis-folded receptor proteins to fold correctly and function properly. Each of those proteins had one of 16 different mutations in the normal 328 amino acid configuration, and all of those mutations involved a single substitution. The scientists treated the proteins with a synthetic antagonist to GnRH, and this antagonist corrected the mutations.



What is the significance of this research?

Like a pinhole aperture on a camera, HH offers a focused vista on several more common protein-folding diseases such as cystic fibrosis, retinitis pigmentosa or hypercholesterolemia.

For further reading:

http://www.the-scientist.com/yr2003/sep/feature_030908.html

http://www.the-scientist.com/yr2002/nov/bunk_p21_021111.html