Drug-like compound stops thyroid overstimulation in early NIH studies

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Researchers at the National Institutes of Health have identified a compound that prevents overproduction of thyroid hormone, a finding that brings scientists one step closer to improving treatment for Graves' disease.

In Graves' disease, the thyroid gland never stops. Thyroid-stimulating antibodies bind to receptors, activating them to keep the thyroid hormone coming and coming — like a broken traffic light stuck on green — and causing the body problems in regulating energy, controlling other hormones and maintaining cells throughout the body.

Attacking the problem at its root cause, lead researcher Susanne Neumann, Ph.D., and her colleagues at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have identified a chemical compound that binds to the receptors and acts as an antagonist, keeping the stimulating antibodies from their work and potentially allowing the thyroid cells to revert to normal function.

The findings, published this month in the *Journal of Clinical Endocrinology and Metabolism*, establish the effect of the receptor antagonist on human thyroid cells. The antagonist has not yet been tested in animals or people and still has multiple steps of toxicology and safety testing before it may be ready for human trials.

Though treatments are available for hyperthyroidism caused by Graves' disease, including surgery, radioactive iodine, and antithyroid drugs, the

relapse rates for these treatments are 5 percent, 21 percent and 40 percent, respectively, and each comes with unfavorable side effects.

"Our goal is to develop an easily produced, orally administered, safe and effective drug with few to no side effects that can be used in place of some of the more invasive treatments of hyperthyroidism caused by Graves' disease," said Marvin Gershengorn, M.D., chief of the Laboratory of Endocrinology and Receptor Biology within NIDDK's intramural research program and the senior author on the paper.

Graves' disease is an autoimmune disorder, causing the body's immune system to act against the body's own cells and organs. Graves' disease typically first occurs in people under 40 and affects approximately 1 percent of the U.S. population, with women five to 10 times more likely than men to have Graves' disease.

The newly discovered compound, which is a receptor antagonist, may have the added benefit of helping those with eye problems caused by Graves' disease — called Graves' ophthalmopathy — experienced by more than 25 percent of people with the disease. Eye problems may include painful swelling in the eye sockets, double vision, tears or itchy eyes, and protruding eyes with swollen eyelids that can't be easily shut, increasing the risk for eye diseases. Because the swelling in the eyes is thought to be associated with the same overstimulation of receptors caused by the same thyroid-stimulating antibodies as in the thyroid, the potential thyroid treatment may have the added benefit of treating the eye problems as well.

The Gershengorn team is also at work on the flip side of thyroid regulation. By researching the thyroid-stimulating hormone receptor, they're hoping to use drug-like compounds to stimulate this receptor to treat people with thyroid cancer, who need more stimulation of thyroid cancer cells to increase the efficacy of iodine radiation. They've tested

their discovery in mice and hope to perform pre-clinical studies and to develop human trials in the foreseeable future.

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