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New insights into treatment of hypothyroidism

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An international research team led by physician-scientists at Rush University Medical Center have gained new insights into hypothyroidism – a condition affecting about 10 million people in the U.S. – that may lead to new treatment protocols for the disease, particularly among the approximately 15 percent of patients for whom standard treatments are less effective.

The researchers published their findings at the beginning of the new year in a pair of articles in the *Journal of Clinical Investigation* (*JCI*) and the *Journal of Clinical Endocrinology & Metabolism* (*JCEM*).

Hypothyroidism occurs when the thyroid gland fails to produce sufficient quantities of two hormones, thyroxine (known as T4) and its more active form, called T3. The condition can cause a number of health problems, including weight gain, fatigue and so-called "foggy brain."

For decades, the standard treatment has been a daily T4 supplement named levothyroxine. Once absorbed into the body, T4 is transformed to T3, in theory fully normalizing blood levels of T3. However, physicians have long been puzzled by why this type of treatment fails to relieve all symptoms in up to 15 percent of patients.

The puzzle persists in large part because the efficacy of treatments for hypothyroidism relies also on patients' subjective reports of how they feel – patients with a normal thyroid may experience symptoms similar to those of hypothyroidism but due to other conditions, such as post-

menopause syndrome or clinical depression.

The study published in the JCI was performed on rats whose thyroid glands had been removed and explains the cellular basis for why circulating levels of T3 are not fully normalized by levothyroxine alone. In addition, the study reveals that circulating T3 levels and hypothyroidism can be corrected fully when the levothyroxine regimen is supplemented with T3.

The study found that some of the rats that only received levothyroxine had higher cholesterol levels in their blood than rats that received the combination T4 and T3 therapy. They also had signs of hypothyroidism in their brains, which could potentially explain the "foggy brain" that is a common symptom of hypothyroidism. Therefore, the combined therapy established normal thyroid hormone action in the areas of the body commonly affected by hypothyroidism—the brain, the liver and also the skeletal muscles.

"Of course it's important to confirm these studies clinically," says Antonio Bianco, MD, PhD, head of Rush's Division of Endocrinology and Metabolism and senior author of both journal articles. Dr. Bianco also co-chaired an American Thyroid Association task force that updated the association's guidelines for the treatment of hypothyroidism published this past December in the journal Thyroid.

"Hypothyroid patients are not all the same. Some will do better on the combination therapy others not. The challenge is to identify these individuals and understand why these differences exist," Dr. Bianco says.

This point was explored in the study published in the JCEM, in which the researchers examined a common polymorphism (a frequent genetic mutation) in the enzyme known as D2 that transforms T4 to T3. In a previous study, hypothyroid patients with this polymorphism preferred

the combination therapy, which led Dr. Bianco and his team to explore the relationship between the polymorphism and the failure of standard therapy for hypothyroidism.

Working with the brains of about 100 cadaver donors, the researchers found that the polymorphic D2 has a tendency to accumulate in a cell compartment that normally does not contain D2. This abnormal accumulation of D2 disrupts cell function in a way also observed in the brain of patients with neurodegenerative diseases such as Huntington disease.

"It is conceivable that the D2 polymorphism is a risk factor for neurodegenerative disease that could be aggravated when these patients develop hypothyroidism," Dr. Bianco says.

Fortunately, treatment may be possible for this condition. "Some of the genes affected by the polymorphic D2 were indicative of oxidative stress," Dr. Bianco says. "When we treated cells containing the polymorphic D2 with a substance that neutralizes oxidative stress, that [treatment] normalized the expression of those genes."

"If confirmed by additional studies, the findings with the D2 polymorphism explain why not all hypothyroid patients are the same, with some exhibiting one or additional risk factors for decreased cognition," Dr. Bianco says. "It would seem that personalized medicine has caught up with hypothyroidism and might be able to ensure that treatment is effective in 100 percent of patients."

Provided by Rush University Medical Center