Thyroid hormone fuels the drive to explore by rewiring brain circuits, new study suggests

August 22 2024

Credit: Pixabay/CC0 Public Domain

Thyroid hormone plays a key role in regulating a range of physiologic functions, including metabolism, temperature, heart rate, and growth. It accomplishes this impressive array of activities by interacting with almost every organ system in the body. Yet despite a long history of research on how thyroid hormone influences different organs, its effects on arguably the most crucial organ—the brain—have remained shrouded

in mystery.

Now, scientists at Harvard Medical School have gained new insights into thyroid hormone's effects on the brain. The work, conducted in mice and published Aug. 22 in *Cell*, shows that thyroid hormone changes the wiring of brain circuits in a manner that drives animals to engage in exploratory behavior.

By simultaneously changing brain wiring and altering metabolic rate, the researchers concluded that thyroid hormone coordinates the brain and body to produce exploratory behavior when it is most needed—for example, during seasons when animals need to find mates or stockpile resources.

"It's well known that thyroid hormone modulates metabolism, and now we've shown that it also modulates exploratory behaviors through direct action on the brain," said lead author Daniel Hochbaum, research fellow in neurobiology in the Blavatnik Institute at HMS.

The findings also help elucidate how low levels of the hormone could lead to depressive states marked by a low desire to explore, while too much could precipitate manic states characterized by an extreme desire for exploration. Thus, the researchers see their work as an important step toward understanding how aberrant levels of thyroid hormone could contribute to certain psychiatric conditions.

Propelled by a personal purpose

Hochbaum's interest in thyroid hormone is a personal one: His wife was diagnosed with hyperthyroidism after experiencing profound and sudden behavioral and metabolic changes. Her symptoms resolved with treatment, but Hochbaum wanted to know more about the hormone's effects on the brain.

"I was really surprised to see that thyroid hormone had large psychiatric effects," Hochbaum said.

He learned that too little thyroid hormone slows down metabolism and can result in symptoms of depression, while too much speeds up metabolism and can lead to symptoms of mania. Yet he couldn't find a satisfactory scientific explanation for how this happens.

During a serendipitous conversation with Bernardo Sabatini, the Alice and Rodman W. Moorhead III Professor of Neurobiology at HMS, Hochbaum found that Sabatini shared his interest in the topic.

"Why thyroid hormone changes behavior has been something that's puzzled me ever since medical school," said Sabatini, who is also director of the Kempner Institute for the Study of Natural and Artificial Intelligence at Harvard University and senior author on the new study. "It was not clear why this hormone should even enter the brain at all."

And with that, a project to explore thyroid hormone's function in the brain was born.

Linking brain, body, and behavior

Thyroid hormone circulates in the bloodstream, traveling to almost every cell and tissue in the body. Its levels are controlled by a complex set of interactions between three players: the thyroid gland, the pituitary gland at the base of the brain, and the hypothalamus, a brain structure located just above the pituitary gland.

However, the receptor for thyroid hormone is expressed by cells throughout the entire brain, including in areas of the cortex responsible for high-level cognition like planning and decision-making.

"What is quite remarkable is that in the adult brain, the thyroid hormone receptor is not only in the hypothalamus, but it's basically everywhere," Hochbaum said.

To investigate why, Hochbaum, Sabatini, and their team performed genetic sequencing on individual cortical cells in mice. They found that the hormone acts on neuronal circuits in the cortex by turning on various genes, essentially changing the wiring of brain cells.

Moreover, when researchers induced higher levels of thyroid hormone in the cortex, mice became more willing to explore the environment and take risks.

Conversely, when researchers blocked the hormone's action in only the cortex, the animals no longer changed how much they explored based on thyroid hormone levels.

"This told us that thyroid hormone is doing important things directly in the cortex," Hochbaum said.

Yet the findings raised a new question: Why would it be beneficial for a hormone that controls metabolism to also alter brain circuits that affect behavior?

To address this question, the researchers turned to previously published field studies that observed behavior in the wild and measured thyroid hormone of lemurs, squirrel monkeys, and other mammals. The research revealed that hormone levels, and in turn metabolic rates, tended to be higher in warmer seasons when food and resources were more abundant—and animals explored more during those seasons.

The studies, combined with the new findings, Hochbaum said, provide an essential missing link between thyroid hormone's effects on the brain

and body.

"We think that thyroid hormone acts directly on brain circuits to coordinate exploratory behaviors with metabolic rate," he added. "It's syncing up your brain and body for the current environment."

Or, as Sabatini put it, "It seems like thyroid hormone prompts the body to tell the brain to go explore and capture resources."

Looking ahead

The way in which thyroid hormone regulates physiology is highly conserved between humans and other mammals, the researchers said, so they suspect that a similar brain-body connection exists in humans.

In fact, a 2024 study led by the same researchers linked higher thyroid hormone levels in U.S. adults to greater employment levels and more hours worked.

The researchers are now exploring this connection in people in Indonesia who experienced the 2004 tsunami. They are interested in whether psychological trauma from the natural disaster has led to long-term changes in thyroid hormone levels.

The team also wants to investigate the basic biology of the exploratory brain circuits that are activated by increased thyroid hormone. The researchers hope that their work could highlight brain circuits relevant to psychiatric conditions such as depression and bipolar disorder.

"The thought is that these conditions are also shaping exploratory activity, so perhaps manipulating thyroid hormone to change brain circuits will reveal relevant points of entry for treatment," Hochbaum said.

More information: Daniel Hochbaum et al, Thyroid hormone remodels cortex to coordinate body-wide metabolism and exploration, *Cell* (2024). DOI: 10.1016/j.cell.2024.07.041.
www.cell.com/cell/fulltext/S0092-8674(24)00835-3