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Defective PTCHD1 gene in brain creates symptoms associated with autism and ADHD

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Evidence is mounting that a gene called PTCHD1 helps the brain sort between important sights and sounds — and distractions. This gene is active in a brain region that attaches more attention to a conversation with your boss, for instance, than to an air conditioner buzzing in the background.

People born with defects in the PTCHD1 gene have been shown in past studies to struggle with sensory overload, as background "noise" leaks into consciousness. This creates a set of symptoms associated with diseases such as autism and ADHD, including attention deficits, aggression and trouble sleeping. Related disabilities affect about one in six American children, but there are currently no treatments for this core distractibility.

Now researchers from NYU Langone Medical Center in New York and Massachusetts Institute of Technology have revealed the mechanisms by which defective PTCHD1 disrupts the nerve circuits that normally sculpt attention by damping down distracting sensory information.

Published in the journal *Nature* March 23, the new study found that mice without PTCHD1 cannot tune out distractions as well as their normal counterparts. The researchers also defined the mechanisms behind these deficits and partly reversed them with an experimental drug.

The study results revolve around the thalamus, the brain region that relays input from the eyes, ears, and skin to the cortex, where they are processed further before driving behavior. Within the thalamus, the PTCHD1 gene is just one of several found recently that, when malfunctioning, affect the thalamic reticular nucleus, or TRN, across diseases that feature attention deficits. Regardless of a diagnosis for autism, ADHD or schizophrenia, an abnormal TRN, the researchers say, may be failing to screen out distracting sensory inputs.

"To our knowledge, this is the first study to detail the biology behind thalamic dysfunction in cognitive disorders caused by PTCHD1 defects in the mammalian brain," says study senior investigator Michael Halassa, MD, PhD, an assistant professor at the Neuroscience Institute at NYU Langone. "We believe that this work defines a new disease category based on common biological signatures surrounding the 'leaky thalamus' and based on a dysfunctional TRN. The field may need to re-think disease definitions to yield more precise treatments."

Leaky Thalamus Drives Core Symptoms

For the newly published study, researchers genetically engineered mice to lack the PTCHD1 gene, which is most active in the TRN as mice develop in the womb. Halassa's lab partnered for the project with Guoping Feng, PhD, at MIT, a world leader in efforts to mimic in mouse models genetic changes that drive human diseases.

The team then measured the ability of their "PTCHD1 knockout" mice to perform tasks that required them to discern between light flashes linked to a food reward and distractions (no reward) when compared to normal mice. By switching the stimulus linked to rewards, the tasks forced the mice to reconsider how much attention they paid to each flash as researchers monitored nerve circuit signaling patterns.

TRN nerve cells in mice without the PTCHD1 gene were found to dampen 25 percent fewer sensory inputs than those in normal mice. With more sensory "noise" leaking through, mice lacking the PTCHD1 gene made three times as many errors in "concentration tests" as normal mice. Furthermore, the behavioral and molecular changes found in the study mice tracked closely with those observed in human patients missing PTCHD1.

In addition to sensory overload, many forms of ADHD and autism, including those linked to PTCHD1 defects, come with sleep disorders. To fall asleep, the brain must pay less attention to sights and sounds. The new study found that the knockout mice had fewer "sleep spindles," EEG patterns known to occur as both mice and humans fall asleep. Such spindles correspond with higher calcium levels, which in turn correlate with more TRN nerve cell firing to suppress sensory inputs.

Given the emerging theory that each day's observations are converted into permanent memories as we sleep, a leaky thalamus may deliver a double hit to learning, say the study authors, distracting patients while awake and subverting memory consolidation while asleep.

The study confirmed that a key consequence of PTCHD1 deletion is reduced calcium levels in TRN nerve cells, with more noise leaking through. The team also partially restored TRN signaling with an experimental drug called 1-ethyl-2-benzimidazolinone that tricks the cells into thinking their calcium levels have returned to normal. While not a candidate for human treatment, the study drug provided the first proof that future drugs may be able to restore nerve cell firing rates to reset thalamic function.

Source:
NYU Langone Medical Center