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Inner-ear disorders may cause hyperactivity

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Behavioral abnormalities are traditionally thought to originate in the brain. But a new study by researchers at Albert Einstein College of Medicine of Yeshiva University has found that inner-ear dysfunction can directly cause neurological changes that increase hyperactivity. The study, conducted in mice, also implicated two brain proteins in this process, providing potential targets for intervention. The findings were published today in the online edition of *Science*.

For years, scientists have observed that many children and adolescents with severe inner-ear disorders – particularly disorders affecting both hearing and balance – also have behavioral problems, such as hyperactivity. Until now, no one has been able to determine whether the ear disorders and behavioral problems are actually linked.

"Our study provides the first evidence that a sensory impairment, such as inner-ear dysfunction, can induce specific molecular changes in the brain that cause maladaptive behaviors traditionally considered to originate exclusively in the brain," said study leader Jean M. Hébert, Ph.D., professor in the Dominick P. Purpura Department of Neuroscience and of genetics at Einstein.

The inner ear consists of two structures, the cochlea (responsible for hearing) and the vestibular system (responsible for balance). Inner-ear disorders are typically caused by genetic defects but can also result from infection or injury.

The idea for the study arose when Michelle W. Antoine, a Ph.D. student

at Einstein at the time, noticed that some mice in Dr. Hébert's laboratory were unusually active – in a state of near-continual movement, chasing their tails in a circular pattern. Further investigation revealed that the mice had severe cochlear and vestibular defects and were profoundly deaf. "We then realized that these mice provided a good opportunity to study the relationship between inner-ear dysfunction and behavior," said Dr. Hébert.

The researchers established that the animals' inner-ear problems were due to a mutation in a gene called Slc12a2, which mediates the transport of sodium, potassium, and chloride molecules in various tissues, including the inner ear and central nervous system (CNS). The gene is also found in humans.

To determine whether the gene mutation was linked to the animals' hyperactivity, the researchers took healthy mice and selectively deleted Slc12a2 from either the inner ear, various parts of the brain that control movement or the entire CNS. "To our surprise, it was only when we deleted the gene from the inner ear that we observed increased locomotor activity," said Dr. Hébert.

The researchers hypothesized that inner-ear defects cause abnormal functioning of the striatum, a central brain area that controls movement. Tests revealed increased levels of two proteins involved in a signaling pathway that controls the action of neurotransmitters: pERK (phosphorylated extracellular signal-regulated kinase) and pCREB (phospho-cAMP response-element binding protein), which is further down the signaling pathway from pERK. Increases in levels of the two proteins were seen only in the striatum and not in other forebrain regions.

To discover whether increased pERK levels caused the abnormal increase in locomotor activity, Slc12a2-deficient mice were given

injections of SL327, a pERK inhibitor. Administering SL327 restored locomotor activity to normal, without affecting activity levels in controls. The SL327 injections did not affect grooming, suggesting that increased pERK in the striatum selectively elevates locomotor activity and not general activity. According to the researchers, the findings suggest that hyperactivity in children with inner-ear disorders might be controllable with medications that directly or indirectly inhibit the pERK pathway in the striatum.

"Our study also raises the intriguing possibility that other sensory impairments not associated with inner-ear defects could cause or contribute to psychiatric or motor disorders that are now considered exclusively of cerebral origin," said Dr. Hébert. "This is an area that has not been well studied."

More information: The paper is titled "A Causative Link Between Inner Ear Defects and Long-term Striatal Dysfunction."

Provided by Albert Einstein College of Medicine