Researchers find explanation for rapid maturation of neurons at birth

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At the moment a newborn switches from amniotic fluid to breathing air, another profound shift occurs: nerve cells in the brain convert from hyperexcitability to a calm frame against which outside signals can be detected.

"Fetal neurons need hyperexcitability for proper development, because they are moving to the right places (in the brain) and forming the right connections," said Wolfgang Liedtke, M.D., Ph.D., assistant professor at the Duke Center for Translational Neuroscience and Klingenstein Fellow in Neuroscience. "But at birth, the brain has to undergo a developmental shift."

It does this by controlling a "pump" that drains chloride out of newborn neurons, making these highly chaotic, developing cells quiet down. Researchers at Duke University Medical Center have figured out the genetic control of the pump in rodents.

These findings may ultimately benefit people who suffer from the neuron misfirings that occur in epilepsy and neuropathic pain, Liedtke said.

"The "chloride shift" is a process that changes newborn neurons and sets the stage for cognition," said Liedtke, who is also an attending physician at Duke Pain Clinics. "It is a fundamental mechanism for brain function ."

The findings were published online in the Journal of Neuroscience on Nov. 19.

The researchers discovered why the pump is almost absent in the developing brain and then goes into high gear after birth: there's a dual-brake mechanism that keeps the chloride-transporter (pump) molecules in check during pregnancy.

Liedtke, lead author Michelle Yeo, Ph.D., and the rest of the team identified a set of DNA repressor elements that act as a pair of brakes. Together the two suppress the gene Kcc2, which is responsible for producing proteins for the transporter molecules that "pump" out the chloride.

The researchers confirmed that increased activity of the gene resulted in lower levels of chloride in the neurons.

Around birth and for a few months afterward, when the brakes are no longer holding fast, Kcc2 makes proteins for the transporter molecules which remain at high levels for a lifetime.

What remains unknown is how the brakes, known as REST (Repressor Element Silencing Transcription) are turned off so Kcc2 can encode for the transporter proteins.

"The research was motivated by trying to understand how the Kcc2 levels are lowered in pathological states like chronic pain and epilepsy," said Yeo, who is a research scientist in the Duke Division of Neurology and author of a landmark study of REST in Science journal. The scientists wanted to create a developmental model that would explain how the pump functions. They also wanted to explore the hyperexcitability of neurons in people with chronic pain and epilepsy, and what makes their neurons revert to this earlier state.

Re-establishing natural inhibition in chronic pain and epilepsy may be a more rational, realistic approach to treatment, Yeo said.

Liedtke also noted that neuron maturation, in terms of the chloride shift, is faster in female rodents. "It's really true that girls mature faster than boys. In rodents, by the three-month mark after birth, there is no difference in chloride levels in neurons. The males catch up."

Source: Duke University Medical Center (news : web)