General anesthetics lead to learning disabilities in animal models

October 22 2009

Studies by researchers at Wake Forest University School of Medicine have shown that blocking the NMDA receptor in immature rats leads to profound, rapid brain injury and disruption of auditory function as the animals mature.

The N-methyl-D-aspartate (NMDA) receptor is activated when a chemical in the brain called glutamate is released by brain cells. This allows calcium to enter into these cells, which can then influence a wide array of important functions. By blocking the receptor, calcium entry is prevented, leading to loss of many of these functions.

Some types of anesthetics used in humans to perform medical procedures act by blocking this receptor, raising the question of whether such anesthetics could produce similar side effects in children exposed to the drugs at a young age.

Whether this is a real clinical issue for children is yet unknown, since all of the School of Medicine's studies on the subject are based on rodent models.

"While research in animals does not always apply to humans, our work with rats supports clinical studies by other groups that suggest learning deficits may occur in young children who have been exposed to general anesthesia," said Christopher P. Turner, Ph.D., an assistant professor of Neurobiology and Anatomy. Turner summarized his latest findings this week at the annual Society for Neuroscience meeting in Chicago. The

summary consisted of back-to-back presentations of five studies using a rodent model of brain injury that have either been published this year in various journals or are scheduled to appear in upcoming issues.

"Over the past decade, we've identified and defined the injuries taking place in young rodent brains, understood the molecular changes that are occurring because of those injuries, and now we understand how those injuries may influence the behavior of laboratory animals that have been exposed to drugs that block the NMDA receptor," Turner said.

Turner and other neuroscientists began considering the potential effects of anesthesia on children after making the connection in animal studies that drugs such as MK801, which act in a similar manner to some general anesthetics by blocking the NMDA receptor, can cause brain injury in immature rodents.

Using rats equivalent in age to children in their last trimester of development through to two years old, the researchers injected MK801, blocking the NMDA receptor in the brain. Within hours, they noticed evidence of injury in many brain regions. The blocking of the receptor, and subsequent inhibition of calcium influx into the cells, caused changes in a variety of proteins critical to normal brain cell function in the rats, particularly communication.

"It's not just that cells are dying," Turner said, "but we have now identified other pathologies that follow from blocking the NMDA receptor. For example, we have found that blocking the receptor results in the turning off of the brain's ability to regenerate new cells, which means that the brain cannot compensate for the cells that die.

"Imagine all of this going on during the time the brain is still developing," Turner added. "With all of these changes, it's not surprising that certain brain functions are diminished as animals get older. For

example, immature animals exposed to MK801 are later unable to respond to auditory cues in a way that would be considered normal. A lot of learning in all animals depends on being able to efficiently process auditory information."

These findings, Turner said, could also have implications for research on schizophrenia. Many of the molecular, cellular and behavioral changes seen in this disorder - NMDA receptor blockade, changes in proteins important for cell-to-cell communication, auditory deficits, and developmental brain injury - are key features of the animal model used by the Turner lab.

"For a long time, researchers have been looking at potential mechanisms trying to figure out the disease, but they've been focused on the adult stages," Turner said. "It has only recently occurred to people that schizophrenia might be a developmental problem. If it's a progressive disease, we may be able to step in at a young age and try to stop it before it is already established and the pathology is locked in."

Source: Wake Forest University Baptist Medical Center (news : web)