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Researchers search for earliest roots of psychiatric disorders

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Newborns whose mothers were exposed during pregnancy to any one of a variety of environmental stressors—such as trauma, illness, and alcohol or drug abuse—become susceptible to various psychiatric disorders that frequently arise later in life. However, it has been unclear how these stressors affect the cells of the developing brain prenatally and give rise to conditions such as schizophrenia, post-traumatic stress disorder, and some forms of autism and bipolar disorders.

Now, Yale University researchers have identified a single molecular mechanism in the developing brain that sheds light on how cells may go awry when exposed to a variety of different environmental insults. The findings, to be published in the May 7 issue of the journal *Neuron*, suggest that different types of stressors prenatally activate a single molecular trigger in brain cells that may make exposed individuals susceptible to late-onset neuropsychiatric disorders.

The researchers found that mouse embryos exposed to alcohol, methyl-mercury, or maternal seizures all activate in the developing brain cells a single gene—HSF1 or heat shock factor—which protects and enables some of the brain cells to survive prenatal insult. Mice lacking the HSF1 gene showed structural brain abnormalities and were prone to seizures after birth, even after exposure to very low levels of the toxins.

In addition, researchers created stem cells—which are capable of becoming many different tissue types, including neurons—from biopsies of individuals diagnosed with schizophrenia. Genes from these

"schizophrenic" stem cells responded more dramatically when exposed to environmental insults than stem cells obtained from non-schizophrenic individuals. The findings provide support to the thesis that stress induces vulnerable cells to malfunction.

"It appears that different types of environmental stressors can trigger the same condition if they occur at the same period of prenatal development," said Yale's Pasko Rakic, senior author of the study. "Conversely, the same environmental stressor may cause different pathologies, if it occurs at different times during pregnancy."

Since HSF1 activation can potentially serve as a permanent marker of the stressed/damaged cell, it opens the possibility of identifying these cells in adults in order to explore the pathogenesis of postnatal disorders and how to protect vulnerable cells.

Provided by Yale University