Preventing the onset of schizophrenia in mouse model

Although predisposing processes occur earlier, schizophrenia breaks out at young adulthood, suggesting it might involve a pathological transition during late brain development in predisposed individuals. Using a genetic mouse model of schizophrenia, researchers from the Caroni group at the Friedrich Miescher Institute for Biomedical Research (FMI) showed that, like in patients, characteristic network and cognitive deficits only emerge in adult mice. They then demonstrated that these deficits could all be permanently prevented by specific treatments during a late adolescence sensitive time window. Their study has been published yesterday in *Cell*.

Schizophrenia – affecting about 1% of the worldwide population – is a mental disorder characterized by disorganized thoughts, false beliefs, difficulty in social relationships, cognitive deficits, abnormal motor behavior, as well as blunted emotions and motivation. A notable feature of this severe, chronic condition is that its symptoms first emerge at the transition between late adolescence and young adulthood. Schizophrenia treatments focus on the symptoms and often consist of antipsychotic medications.

The causes of schizophrenia are complex. They include comparable contributions by environmental factors – such as problems during birth, psychosocial factors, stress, and the consumption of cannabis during adolescence – and genetic factors, which in most cases involve mutations in large numbers of genes, each making a small contribution to the condition.

Using a genetic mouse model

In order to do research on the root causes of a condition with a complex genetic component, researchers need to focus, if possible, on simpler ‘genetic models’ – people or animals with well-defined mutations exhibiting a strongly elevated risk of developing the disease. In schizophrenia, such models include people with the 22Q11DS syndrome, caused by deletions within a segment of chromosome 22, who have a 20 to 30-fold increased risk of developing schizophrenia. This led researchers to develop mice carrying a corresponding deletion in order to use them as a model of schizophrenia for lab research. (These mice are called “LgDel mice” but for simplicity reasons we will call them “schizophrenia-mice” here.)

Using the schizophrenia mouse model, researchers from the Caroni group set out to investigate the deficits exhibited by the schizophrenia-mice, and how these could be treated and perhaps prevented. The researchers showed that what was already known in human patients was also true in the schizophrenia-mice: network and cognitive dysfunctions emerged after late adolescence. Like patients, adult mice showed profound dysfunctions in a particular type of neurons called PV neurons, which are important orchestrators of neural networks. The dysfunctions led to network synchronization deficits, a hallmark of schizophrenia. Notably, antipsychotic drugs temporarily suppressed network and cognitive deficits in adult schizophrenia-mice.

Permanently preventing the onset of schizophrenia

Although PV neuron dysfunctions only spread through the brain in the adult, they were already present in the hippocampus of adolescent schizophrenia mice. Since late adolescence represents a time window when coordinated activity depending on hippocampal and cortical PV neurons is important for late brain maturation, the Caroni group hypothesized that adolescent hippocampal dysfunctions might interfere with proper brain maturation in schizophrenia-mice. The researchers investigated whether they could prevent the onset of
They succeeded! They showed that repeated treatments targeting the hippocampal PV network with common antipsychotic drugs or with more specific genetic activators of PV neurons, during 6-10 days, at the transition between late adolescence and adulthood, produced a complete and long-lasting rescue of network dysfunctions, as well as cognitive deficits in adult schizophrenia-mice.

“Our findings in a genetic mouse model support the hypothesis that a critical developmental time window influences the emergence of schizophrenia at the transition between late adolescence and adulthood – and that it is possible to prevent the progression of schizophrenia by treatment during that time window,” says Pico Caroni. “It might be possible to build on our study to develop therapeutic strategies to prevent the outbreak of schizophrenia in at risk individuals.”

Original publication

Arghya Mukherjee, Fernando Carvalho, Stephan Eliez, Pico Caroni (2019). Long-lasting rescue of network, cognitive dysfunction in genetic schizophrenia model. Cell, advance online publication.

Contact

Pico Caroni, pico.caroni@fmi.ch, Tel: + 41 (0)61 697 37 27

Pico Caroni is a senior group leader at the FMI and Professor of Neurobiology at Basel University. Caroni is one of the world’s leading neurobiologists studying how changes in the brain are related to learning and memory. He and his research group are also interested in how these processes are impaired in mental disorders.

» More about the Caroni group

About the FMI

The Friedrich Miescher Institute for Biomedical Research (FMI), based in Basel, Switzerland, is a world-class biomedical research institute dedicated to understanding the molecular mechanisms of health and disease. Its main areas of expertise are neurobiology, quantitative biology and epigenetics. With a staff of about 350, the FMI offers an exceptional training environment for PhD students and postdoctoral fellows from around the world. The FMI is affiliated with the University of Basel and the Novartis Institutes for BioMedical Research, and is currently being co-led by Prof. Silvia Arber and Prof. Dirk Schübeler.

» More about the FMI