Protein researches closing in on the mystery of schizophrenia

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(Medical Xpress)—Schizophrenia is a severe disease for which there is still no effective medical treatment. In an attempt to understand exactly what happens in the brain of a schizophrenic person, researchers from the University of Southern Denmark have analyzed proteins in the brains of rats that have been given hallucinogenic drugs. This may pave the way for new and better medicines.

Seven per cent of the adult population suffers from schizophrenia, and although scientists have tried for centuries to understand the disease, they still do not know what causes the disease or which physiological changes it causes in the body. Doctors cannot make the diagnosis by looking for specific physiological changes in the patient's blood or tissue, but have to diagnose from behavioral symptoms.

In an attempt to find the physiological signature of schizophrenia, researchers from the University of Southern Denmark conducted tests on rats, and they now believe that the signature lies in some specific, measurable proteins. Knowing these proteins and comparing their behaviour to proteins in the brains of not schizophrenic people may make it possible to develop more effective drugs.

It is extremely difficult to study brain activity in schizophrenic people, which is why researchers often use animal models in their strive to understand the mysteries of the schizophrenic brain. Rat brains resemble human brains in so many ways that it makes sense to study them if one wants to learn more about the human brain.

Schizophrenic symptoms in rats

The strong hallucinogenic drug phenocyclidine (PCP), also known as "angel's dust", provides a range of symptoms in people which are very similar to schizophrenia.

"When we give PCP to rats, the rats become valuable study objects for schizophrenia researchers," explains Ole Nørregaard Jensen, professor and head of the Department of Biochemistry and Molecular Biology.

Along with Pawel Palmowski, Adelina Rogowska-Wrzesinska and others, he is the author of a scientific paper about the discovery, published in the international *Journal of Proteome Research*.

Among the symptoms and reactions that can be observed in both humans and rats are changes in movement and reduced cognitive functions such as impaired memory, attention and learning ability.

"Scientists have studied PCP rats for decades, but until now no one really knew what was going on in the rat brains at the molecular level. We now present what we believe to be the largest proteomics data set to date," says Ole Nørregaard Jensen.

PCP is absorbed very quickly by the brain, and it only stays in the brain for a few hours. Therefore, it was important for researchers to examine the rats' brain cells soon after the rats were injected with the hallucinogenic drug.

"We could see changes in the proteins in the brain already after 15 minutes. And after 240 minutes, it was almost over," says Ole Nørregaard Jensen.

The University of Southern Denmark holds some of the world's most

advanced equipment for studying proteins, and Ole Nørregaard Jensen and his colleagues used the university's so-called mass spectrometres for their protein studies.

352 proteins cause brain changes

"We found 2604 proteins, and in 352 of them, we saw changes that can be associated with the PCP injections. These 352 proteins will be extremely interesting to study in closer detail to see if they also alter in people with schizophrenia - and if that's the case, it will of course be interesting to try to develop a drug that can prevent the protein changes that lead to schizophrenia," says Ole Nørregaard Jensen about the discovery and the work that now lies ahead.

The 352 proteins in rat brains responded immediately when the animals were exposed to PCP. Roughly speaking, the drug made proteins turn on or off when they should not turn on and off. This started a chain reaction of other disturbances in the molecular network around the proteins, such as changes in metabolism and calcium balance.

"These 352 proteins are what causes the rats to change their behaviour - and the events are probably comparable to the devastating changes in a schizophrenic brain," explains Ole Nørregaard Jensen.

The protocol for studying rat brain proteins with mass spectrometry, developed by Ole Nørregaard Jensen and his colleagues, is not limited to schizophrenia studies - it can also be used to explore other diseases.

The research was a collaboration between the University of Southern Denmark, the Danish Technological Institute and NeuroSearch A/S.

Details about the experiment

Twelve rats were used for the experiment. Six received an injection with the hallucinogenic drug PCP (10 mg/kg body weight), and six were injected with a saline solution to serve as controls. After 15 minutes, the first two animals in each group were killed and within less than two minutes, samples of their brains (temporal lobes) were taken and quickly frozen in liquid nitrogen.

After 30 and 240 minutes, respectively, the same was done to other rats. All experiments were conducted in accordance with Danish and EU guides for the handling of laboratory animals. The collected tissue samples were then subjected to various mass spectrometric protein analyses. The analyses revealed differences in the phosphorylation of proteins indicating which proteins had been affected by the drug PCP.

Interpretation of the complex protein data set suggest that PCP affects a number of processes in brain cells and leads to changes in calcium balance in the brain cells, changes in the transport of substances into and out of cells, changes in cell metabolism and changes in the structure of the cell's internal skeleton, the cytoskeleton.

More information: Acute Phencyclidine Treatment Induces Extensive and Distinct Protein Phosphorylation in Rat Frontal Cortex. Palmowski P, Rogowska-Wrzesinska A, Williamson J, Beck HC, Mikkelsen JD, Hansen HH, Jensen ON. J Proteome Res. 2014 Feb 24. www.ncbi.nlm.nih.gov/pubmed/24564430

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