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Brain compound 'throws gasoline onto the fire' of schizophrenia

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New research has traced elevated levels of a specific compound in the brain to problem-solving deficits in patients with schizophrenia.

The finding suggests that drugs used to suppress the compound, called kynurenic acid, might be an important supplement to antipsychotic medicines, as these adjuncts could be used to treat the disorder's most resistant symptoms – cognitive impairments.

Though schizophrenia is commonly characterized by hallucinations and delusions, patients also have problems with what is known as cognitive flexibility or executive decision-making. Many patients can set a goal and plan one way to achieve it, but cannot adjust their thinking if circumstances force them to consider alternative strategies.

"We've got this core cluster of symptoms that is the Achilles heel for these individuals, and we're not really doing a good job of treating them," said John P. Bruno, professor of psychology, psychiatry and neuroscience at Ohio State University and principal investigator of the research.

Bruno and colleagues have combined advanced animal modeling of schizophrenia-related chemical changes in the brain with the observation that the production of too much kynurenic acid is linked to troubled thinking that affects the research animals' behavior.

The compound is present in all human brains and has some useful

functions. But in excessive amounts, the researchers found, kynurenic acid interferes with other chemical processes that govern the ability to pay attention and think strategically under changing conditions.

"If we try to make predictions about how disabled patients with schizophrenia will be and how likely are they to be integrated into the social fabric, it's the severity of the cognitive deficits that are most predictive," Bruno said. "Antipsychotics are particularly good at what we call positive symptoms, but these same drugs are very poor at treating the cognitive deficits.

"There are a lot of therapeutic strategies for dealing with schizophrenia, but one which has not been explored, and which we think has a great deal of promise, has to do with regulating production of kynurenic acid," Bruno said.

He described the research Tuesday (11/18) at the Society for Neuroscience meeting in Washington, D.C.

Bruno and colleagues tested kynurenic acid's effects on cognitive abilities in rats. Seven rats were given a compound that stimulated excess production of the molecule in their brains, while a control group of rats received no such stimulation. All of the rats were subjected to a test gauging their ability to make what is called an extra-dimensional set shift, requiring them to change response strategies based on changing contingencies – in this case, in a quest to find food.

Only 28 percent of the rats with elevated kynurenic acid were able to solve problems to receive a food reward, compared to 100 percent of the control animals. Before the intervention, all of the animals were equally able to find the food under changing circumstances.

The kynurenic acid essentially exacerbates a phenomenon already

observed in patients with schizophrenia – the fact that two neurotransmitters in their brains are not as active as they need to be to allow for normal problem-solving capabilities.

These two neurotransmitters critical to normal cognition are acetylcholine and glutamate. Their activity is partially regulated by what are called alpha-7 receptors, a class of proteins involved in the brain's chemical communication system. In the case of schizophrenia, these neurotransmitters are already at abnormally low levels, most likely because of genetic mutations.

Excess levels of kynurenic acid inhibit the work of the alpha-7 receptors, meaning they suppress the release of these neurotransmitters even more.

"So we've already got problems with these neurotransmitters, and then to make matters worse, we've got all this extra kynurenic acid antagonizing the alpha-7 receptors, which just throws gasoline onto the fire," Bruno said. "If we can design drugs that are able to inhibit the enzymes that are responsible for overproducing kynurenic acid, we may improve cognitive performance in these patients."

Antipsychotic agents used to control hallucinations and delusions act on different neurotransmitters. Agents targeting kynurenic acid production could be part of a medication cocktail that could restore additional neurochemistry responsible for cognition, Bruno said.

Bruno's research group is able to precisely gauge the effects of the compound on neurotransmitters in the brain because of the animal model used for the research. Schizophrenia was once considered too complex a disorder to model in an animal brain, but Bruno and colleagues have developed a rat model to focus on specific cognitive deficits traced to the part of the brain known as the prefrontal cortex.

An element of the modeling is the painless use of microelectrodes in the animals' brains to measure neurotransmitter levels before and after introduction of the agent that elevates kyurenic acid. The real-time measurements allow the scientists to prove the causal relationship between the elevated compound and the reduced presence of the neurotransmitters.

"No one is claiming that we're producing rats with schizophrenia. What we can do is model the neural side pathologies and see if those pathologies lead to behavioral impairments that look like what see on the clinical side. When we get both of those to line up as we have in this model, we have a valid model to ask questions about developing novel therapeutics," Bruno said. "This has allowed us to move from molecules to neurotransmitters to cognitive behavior all in one fell swoop. These findings set the foundation for several years of research that we hope will have some very big implications."

Source: Ohio State University