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Some antipsychotic drugs may be missing their mark

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Drugs that treat depression, schizophrenia and other psychotic conditions and that target a particular protein on brain cells might not be triggering the most appropriate response in those cells, new research suggests.

The study by researchers at The Ohio State University Medical Center examined the serotonin 2A receptor, a protein on brain cells sensitive to the neurotransmitter serotonin.

This study examined the early chemical events that happen inside neurons when the 2A receptor is stimulated by serotonin and by a synthetic hallucinogenic agent that is thought to mimic serotonin.

The findings, published online in the early edition of the *Proceedings of the National Academy of Sciences* with an accompanying editorial, show that although both compounds combine with and activate this receptor, they trigger different chemical pathways inside the neuron.

Researchers say that the work could have important implications for the development of drugs that affect the serotonin 2A receptor, a key target in the treatment of several important mental disorders.

“This new insight into how serotonin and a hallucinogenic drug affect this serotonin receptor could lead to changes in how new drugs are screened and developed for depression, schizophrenia and other neuropsychiatric disorders,” says study leader Laura M. Bohn, an associate professor of pharmacology and psychiatry.

Currently, it is thought that when serotonin binds with the receptor, it sends a signal that activates molecules inside the cell called G proteins.

This study shows, however, that the receptor responds to serotonin by also activating a protein called beta-arrestin inside the cell. The synthetic hallucinogen, on the other hand, causes the receptor to activate only the G proteins. The hallucinogen does not seem to use beta-arrestins to cause its effects.

For this study, Bohn and her colleagues used laboratory-grown cells and a strain of mice that lacked beta-arrestin. The hallucinogen was a hallucinogenic amphetamine called DOI.

When the researchers injected normal (i.e., control) and experimental mice with DOI, both groups showed a head-twitch behavior, a characteristic response in mice to hallucinogens.

But when the mice were given high doses of serotonin, which typically also causes the head-twitch behavior, the behavior occurred in the control animals only, and not in the mice lacking beta-arrestin.

“That demonstrates that the signal for serotonin requires beta-arrestin for that biological effect,” Bohn says. “The synthetic hallucinogen, on the other hand, induces the head-twitch behavior whether beta-arrestin is present or not.

“Overall, our findings suggest that the screening of agents intended to be serotonin mimics must also determine if the agent signals through beta-arrestin,” Bohn says. “That isn’t done now.”

Source: Ohio State University