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Looking beyond the drug receptor for clues to drug effectiveness

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Antipsychotic drugs that are widely used to treat schizophrenia and other problems may not work as scientists have assumed, according to findings from Duke University Medical Center researchers that could lead to changes in how these drugs are developed and prescribed.

Scientists have known that all antipsychotic drugs target the D2 receptor inside cells. New tests developed at Duke reveal that the biochemical pathways linked to this receptor – the pathways along which the drugs deliver their therapeutic effects – may function differently than previously understood.

The Duke team developed specialized tests and studied two main pathways that stem from the receptor. The first is the G-protein-dependent signaling pathway, and the other is the beta arrestin pathway.

Most antipsychotic drugs in use today were developed to target the G-protein signaling that occurs at the receptor. Only recently, beta-arrestin, a protein known as an "off-switch" for G-protein receptors, has been shown to also play a role in directing other cellular activities.

The tests uncovered surprising results. "Our work showed that all nine antipsychotic drugs we examined uniformly and more potently block the beta-arrestin pathway downstream of the D2 dopamine receptor," said Bernard Masri, Ph.D., lead author and postdoctoral researcher in the Duke Department of Cell Biology.

The drugs, however, showed a variety of effects at the G-protein pathway. "Some activated it, some blocked the G side totally, some blocked it only 50 percent – the drugs had different profiles for the G-protein pathway," Masri said. "So with this new information, drug manufacturers would want to make sure new compounds for antipsychotic use block the beta-arrestin pathway."

There may be even more pathways not yet known to flow from the D2 receptor, he added, pointing up the difficulty of developing a drug with the greatest possible effectiveness and fewest side effects. To further complicate the situation, antipsychotic drugs also work on receptors other than the D2 receptor. The drugs are used mainly to treat schizophrenia, which affects about 1 percent of people in the United States.

G-protein coupled receptors have been the most common target of such therapeutic drugs. The findings about beta arrestin's dual role open possibilities for developing new drugs. The importance of this concept for G-protein coupled receptors, especially the dopamine receptor, was demonstrated at Duke by the acclaimed receptor pioneer Robert J. Lefkowitz, M.D., and Marc G. Caron, Ph.D., the senior author on the current study.

"This work with antipsychotic drugs represents an entirely new approach for studying drug effects and developing new ones," Masri said of the Duke team's research, published the week of Aug. 25-29 in the *Proceedings of the National Academy of Sciences*.

In this study, the scientists used a technique called bioluminescence resonance energy transfer (BRET) in cells in culture. "Using cells to monitor specific receptor signaling pathways could provide more selective medicines with fewer side effects," said co-author Ali Salahpour, Ph.D., also a postdoctoral researcher in cell biology. "This is

where pharmaceutical research is headed."

BRET is a luminescence-based technique that monitors interactions between molecules. One assay in this study followed the variation of cyclic adenosine monophosphate to look at the G-protein dependent pathway, and the other measured the direct interaction of beta arrestin with the dopamine D2 receptor. The antipsychotics were tested with both assays to look at which pathway(s) they were activating or blocking, and with what strength and efficacy.

Marc Caron, Ph.D., James B. Duke Professor in the Department of Cell Biology and director of the research laboratory, said, "Using these assays as a means to develop antipsychotics should be a useful way to target precise responses and improve patient symptoms." Unwanted side-effects, such as spasms or movement problems that cause the whole body or parts of the body to move uncontrollably, are associated with some of the antipsychotic drugs studied.

"Not all drugs used for schizophrenia have the same degree of movement-related side effects," Caron said. "For some of the drugs, these side effects may stem from interactions on the G protein part of the pathways." Therefore, evaluating antipsychotic drugs early that act less or not at all on the G side, but are effective on the beta arrestin side, could provide improved efficacy with many fewer side effects.

The next project for the scientists is to study these drugs and the relevant pathways in both normal mice and mice with traits of psychosis.

Source: Duke University