[News Article on a Biology Publication]

Uncovering How Antipsychotic Medications Cause Weight Gain

Since the development of antipsychotic medications in the 1950s, their side effects have limited their potential to relieve suffering in people with schizophrenia, bipolar disorder, and other mental illnesses. A recent study led by Solomon Snyder, MD, professor of neuroscience at Johns Hopkins University, sheds light on the mechanism of how the most commonly prescribed antipsychotics cause weight gain. The discovery could lead to improvements in therapy, as Dr. Snyder explained: "Our identification of the molecular players that link such drugs to increased food intake means there's now hope for finding a newer generation of drugs without the weight-gain side effects."

The early antipsychotic drugs, such as chlorpromazine (Thorazine) and haloperidol (Haldol), are relatively effective at reducing forms of psychosis such as hallucinations, disorganized behavior, and delusions (strongly held false beliefs). However, these first generation or "typical" antipsychotics can cause abnormal movements, such as tremor, involuntary contortions, and restless motion. The newer "atypical" antipsychotic drugs, so called because they do not cause these movement disorders, have long been preferred over the older antipsychotics. But the atypical medications have been limited by a different set of side effects: weight gain, high cholesterol, and diabetes. In the interest of developing medications with fewer side effects, scientists in the field have focused on the mechanism behind these effects.

Among the atypical agents, olanzapine (Zyprexa) and clozapine (Clozaril) are most strongly associated with weight gain. One analysis from 2003 reported that olanzapine caused a gain of more than 7% body weight in 30% of patients. The recent article by Dr. Snyder's group, published in *Proceedings of the National Academy of Sciences of the USA*, reported that appetite-stimulating antipsychotic drugs activate an enzyme in the body that has been linked to appetite regulation. This enzyme (a chemical that makes it easier for other chemicals to react with each other) is called adenosine monophosphate–kinase or AMPK. Dr. Snyder's

group also found that activation of this AMPK is triggered in turn by blocking a particular receptor on the surface of cells, the histamine-1 receptor.

These research findings point to possible strategies for reducing weight gain from atypical antipsychotic medications. For example, one might be combine these agents with drugs that stimulate the histamine-1 receptor or attempt to develop new, related antipsychotics that are less likely to block the receptor.

Dr. Snyder's group made their discovery first by testing the mouse hypothalamus—a section of the brain that regulates the pituitary gland, which in turn regulates hunger, body temperature, and other functions. They placed slices of the mouse hypothalamus in two atypical antipsychotics, olanzapine and clozapine. Each drug caused an increase in the concentration and activity of the AMPK enzyme within the hypothalamus. However, placing the hypothalamus slices in other antipsychotic drugs that are less appetite-stimulating did not increase the concentration or activity of AMPK. Then, to further explore these findings, the scientists injected mice with clozapine or olanzapine. These injections increased the concentration of AMPK in the hypothalamus and increased its activity by four times. On the other hand, when the drugs were administered to a strain of mice that lacked the histamine-1 receptor, there was no weight gain and no increase in the level or activity of AMPK. Therefore, blocking the histamine 1 receptor was a necessary step in the process that allowed the drugs to influence AMPK and then weight gain.

"Histamine has a long history as a suspect in weight control, but no one ever could put a finger on the exact link," Dr. Snyder said. "The connection we've made between its receptor and appetite control is incredibly intriguing and opens new avenues for research on weight control, possibly including drugs that suppress appetite safely."

The researchers went on to study the effect of clozapine after giving the mice leptin, an appetite suppressant known to reduce AMPK activity in the hypothalamus. Here, clozapine reversed the effects of leptin: causing AMPK activity to rise again.

Based on these findings, the group concluded that appetite stimulation from atypical antipsychotic drugs is caused by their blocking of the histamine-1 receptor, which then causes activation of the enzyme AMPK, which then leads to weight gain (diagrammed in the **Figure** below).

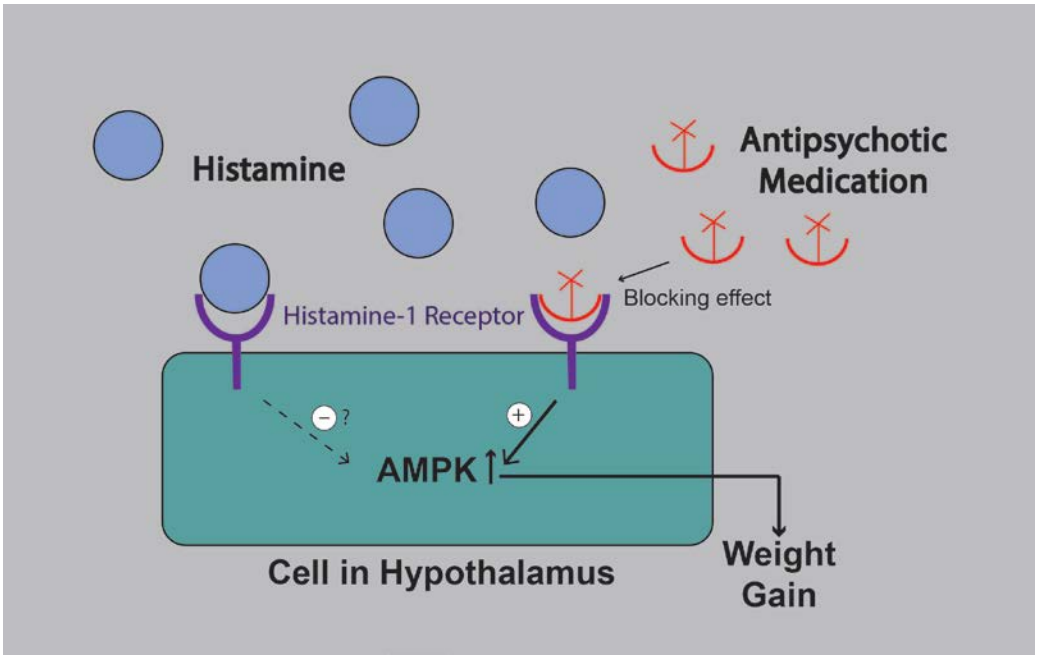

Figure. Certain antipsychotic medications block the histamine-1 receptor, which increases the concentration and activity of the enzyme AMPK in the hypothalamus, and this leads to weight gain. Strategies that stop the antipsychotics from blocking the histamine receptor, such as drugs that act like histamine in the hypothalamus, could prevent the weight gain caused by antipsychotics. (Figure by Seth Karten)

There has been some debate in the scientific literature about the mechanism of appetite increase by antipsychotic medications. Various reports have suggested that the mechanism involves other chemical receptors or enzymes, such as serotonin receptors, dopamine receptors, or the liver enzyme cytochrome P450. However, one study found that among 17 antipsychotic agents, those that caused the most weight gain had the strongest tendency to bind to the histamine-1 receptor.

The report by Dr. Snyder's group strongly supports the argument that the histamine-1 receptor plays a crucial role in weight gain caused by atypical antipsychotics, and weight gain in general. This discovery may lead to improvements in the treatment of schizophrenia, other mental illnesses, and even obesity unrelated to antipsychotic medications.