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What is the mechanism for aripiprazole's effect on reducing olanzapine-associated obesity?

Abstract

We read with great interest Henderson and colleagues' paper in your journal (2009; 29:165–169), which reported that aripiprazole reduced olanzapine-induced overweight/obesity and hyperlipidemia in a 10-week placebo-controlled double-blind crossover study. This and their previous studies, provide a new way for controlling olanzapine- and clozapine-induced weight gain/obesity using another atypical antipsychotic, even without reducing the original olanzapine and clozapine doses, which is important particularly for treatment of refractory schizophrenia patients.

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Letter to Editors:

Title: What is the mechanism for aripiprazole's effect on reducing olanzapine-induced obesity?

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Conflict of Interest:

All authors declare that they have no conflicts of interest.

Running title: Aripiprazole, dopamine D2 receptor; obesity

Editors,

We read with great interest Henderson and colleagues' paper in your journal (2009; 29:165–169), which reported that aripiprazole reduced olanzapine-induced overweight/obesity and hyperlipidemia in a 10-week placebo-controlled double-blind crossover study. This and their previous studies ^{1,2} provide a new way for controlling olanzapine- and clozapine-induced weight gain/obesity using another atypical antipsychotic, even without reducing the original olanzapine and clozapine doses, which is important particularly for treatment of refractory schizophrenia patients. The key issue is what are the mechanisms that underlie aripiprazole's effects on body weight? Henderson et al. proposed that aripiprazole's low histaminergic antagonism and 5-HT_{2C} agonist activity may contribute to its effect on reducing olanzapine-induced weight gain ¹.

Several meta-analytical studies have indicated an association between histamine H1 antagonism properties in antipsychotic drugs and obesity side-effects ^{3,4}. Consistent with these findings, both olanzapine and clozapine are potent H1 antagonists ⁵. A recent study found that, correlated with body weight gain, olanzapine treatment significantly down-regulated H1 receptor binding and mRNA expression in the rat hypothalamus, however, aripiprazole did not affect H1 receptor expression ⁶. These results suggest that aripiprazole's effects in reducing olanzapine- and clozapine-induced weight gain/obesity should not be via H1 receptors, although histaminergic antagonism is a main cause of olanzapine- and clozapine-induced weight gain/obesity.

We agree that 5-HT_{2C} receptors may play a role, however, it should also be noted that aripiprazole has only a moderate affinity to 5-HT_{2C} receptors ⁷. Aripiprazole was

developed as a potent dopamine D2 partial-agonist, 5-HT_{1A} partial agonist, and also 5-HT_{2A} antagonist⁷. A recent study has reported that both aripiprazole and olanzapine affect 5-HT_{1A} receptor expression, but these changes are not correlated with body weight⁸. On the other hand, like aripiprazole, olanzapine and clozapine are 5-HT_{2A} antagonists⁵. Recent studies have suggested that aripiprazole is not a simple partial agonist, but a functionally selective drug that can act as a D2 agonist or D2 antagonist in different brain regions^{9,10}. We suggest that aripiprazole's D2 agonistic property may account partly for the effect of aripiprazole in reducing olanzapine-induced overweight /obesity. Atypical antipsychotics such as olanzapine may increase appetite through the dopamine-mediated reward pathway¹¹. Dopamine D2 agonists have been reported to reduce food intake by acting in hypothalamic areas¹².

Another possible mechanism of aripiprazole may be via the activation of the PI3K/Akt pathway. The PI3K/Akt pathway plays an important role in cellular proliferation, growth and metabolism¹³. Over-expression of the pathway causes cancer but defects in the pathway could induce metabolic disorders. The PI3K/Akt pathway plays a key role in the action of insulin via control of Glu4, which transports glucose into the cells¹⁴. The activity of the PI3K/Akt pathway in insulin-mediated Glu4 activation is impaired in olanzapine-induced obesity¹⁵. Aripiprazole may have an effect on the activation of the PI3K/Akt pathway via its agonistic effect on D2 receptors. In fact, D2 receptor agonist (bromocriptine) has been reported to increase the PI3K/Akt pathway activity¹⁶. It is possible that aripiprazole can restore the impairment of the PI3K/Akt pathway in insulin-mediated Glu4 activation caused by olanzapine so that the side-effect of weight gain is reduced. Further studies on these

mechanisms will improve our understanding and management of atypical antipsychotic-induced weight gain/obesity.

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