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

Chao Deng  
*University of Wollongong, chao@uow.edu.au*

J-Z Chen  
*University of Wollongong, jiezhong@uow.edu.au*

Changhua Hu  
*University of Wollongong*

Xu-Feng Huang  
*University of Wollongong, xhuang@uow.edu.au*

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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?

Authors: Chao Deng, PhD$^{1,2}$, Jiezhong Chen, PhD, MD$^1$, Changhua Hu, PhD$^{1,3}$, Xu-Feng Huang, PhD, MD$^{1,2}$
1: Centre for Translational Neuroscience, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia
2: Schizophrenia Research Institute, 384 Victoria Street, Darlinghurst, 2010, NSW, Australia
3: School of Pharmaceutical Sciences, Southwest University, Chongqing 400716, China

Corresponding author:

Dr Chao Deng, School of Health Sciences, University of Wollongong, Wollongong, 2522, NSW, Australia
E-mail: chao@uow.edu.au, Tel: (+61 2) 4221 4934, Fax: (+61 2) 4221 4096

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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-HT2C 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-HT2C receptors may play a role, however, it should also be noted that aripiprazole has only a moderate affinity to 5-HT2C receptors 7. Aripiprazole was
developed as a potent dopamine D2 partial-agonist, 5-HT$_{1A}$ partial agonist, and also
5-HT$_{2A}$ antagonist. A recent study has reported that both aripiprazole and olanzapine
affect 5-HT$_{1A}$ receptor expression, but these changes are not correlated with body
weight. On the other hand, like aripiprazole, olanzapine and clozapine are 5-HT$_{2A}$
antagonists. 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. 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 pathway. Dopamine D2 agonists have been
reported to reduce food intake by acting in hypothalamic areas.

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 metabolism. 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 cells. The activity of the PI3K/Akt pathway in insulin-mediated
Glu4 activation is impaired in olanzapine-induced obesity. 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 activity. 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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