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Chronic olanzapine activates the Stat3 signal transduction pathway and alters expression of components of the 5-HT_{2A} receptor signaling system in rat frontal cortex☆

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Abstract

The mechanisms underlying desensitization of serotonin 2A (5-HT_{2A}) receptor signaling by antagonists are unclear but may involve changes in gene expression mediated via signal transduction pathways. In cells in culture, olanzapine causes desensitization of 5-HT_{2A} receptor signaling and increases the levels of regulators of G protein signaling (RGS) 7 protein dependent on phosphorylation/activation of the Janus kinase 2 (Jak2)/signal transducers and activators of transcription 3 (Stat3) signaling pathway. In the current study, the 5-HT_{2A} receptor signaling system in rat frontal cortex was examined following 7 days of daily treatment with 0.5, 2.0 or 10.0 mg/kg i.p. olanzapine. Olanzapine increased phosphorylation of Stat3 in rats treated daily with 10 mg/kg olanzapine and caused a dose-dependent desensitization of 5-HT_{2A} receptor-mediated phospholipase C activity. There were dose-dependent increases in the levels of membrane-associated 5-HT_{2A} receptor, $G_{\alpha 11}$ and $G_{\alpha q}$ protein levels but no changes in the G_{β} protein levels. With olanzapine treatment, RGS4 protein levels increase in the membrane-fraction and decrease in the cytosolic fraction by similar amounts suggesting a redistribution of RGS4 protein within neurons. RGS7 protein levels increase in both the membrane and cytosolic fractions in rats treated daily with 10 mg/kg olanzapine. The olanzapine-induced increase in Stat3 activity could underlie the increase in RGS7 protein expression in vivo as previously demonstrated in cultured cells. Furthermore, the increases in membrane-associated RGS proteins could play a role in desensitization of signaling by terminating the activated $G_{\alpha q/11}$ proteins more rapidly.
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1. Introduction

Adaptive changes in post-synaptic serotonin2A/2C (5-$HT_{2A/2C}$) receptor signaling may underlie the mechanism of action of several drug treatments for neuropsychiatric disorder (Roth et al., 1998). For example, several antipsychotic drugs, such as olanzapine, desensitize both 5-HT_{2A} and 5-HT_{2C} receptors (Roth et al., 1998) while 5-HT uptake blockers (e.g., fluoxetine), can increase the maximal efficacy of 5-HT_{2A} receptor signaling (Damjanoska et al., 2003; Tilakaratne et al., 1995). These adaptive changes may explain the 2–3 week delay in full symptom improvement seen with these drug treatments. However, the molecular mechanisms that underlie these adaptive changes in 5-HT_{2A} receptor signaling are not well understood.

Treatment with many 5-HT_{2A} receptor antagonists including olanzapine causes a decrease in the density of 5-HT_{2A} receptor binding sites with no change in K_D in rat frontal cortex and in cells in culture (Anji et al., 2000; Kusumi et al., 2000; Tarazi et al., 2002; Willins et al., 1999). Consistent with these findings, 5-HT_{2A} receptor antagonists including clozapine and

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olanzapine cause 5-HT_{2A} receptor internalization, i.e., redistribution of 5-HT_{2A} receptors from plasma membrane to within cell bodies, both in vivo and in cells in culture (Bhatnagar et al., 2001; Willins et al., 1999). Internalization of a number of receptors, including 5-HT_{1A} receptors and m1 muscarinic receptors, leads to activation of signal transduction pathways (Pierce and Lefkowitz, 2001). Sustained activation of specific intracellular signal transduction pathways, such as the Jak/Stat pathway, as would occur following internalization of 5-HT_{2A} receptors induced by chronic antagonist treatment, could then lead to changes in gene expression and long-term changes in the 5-HT_{2A} receptor signaling system. This receptor system is composed of 5-HT_{2A} receptors that are coupled via $G_{\alpha q/11}$ proteins to increase the activity of phospholipase C (PLC) (Roth et al., 1998). Hydrolysis and thereby termination of 5-HT_{2A} receptor-activated $G_{\alpha q/11}$ protein signaling is enhanced by RGS4 and RGS7 proteins (Ghavami et al., 2004; Shuey et al., 1998).

The Jak/Stat pathway is activated by a number of G protein coupled receptors such as 5-HT_{2A}, β2-adenoreceptors and angiotensin II receptors (Guillet-Deniau et al., 1997; Ram and Iyengar, 2001). Activation of 5-HT_{2A} receptors causes a rapid and transient activation of Jak2 and Stat3 (Guillet-Deniau et al., 1997). Serotonin stimulation also induced the co-immunoprecipitation of Stat3 with Jak2 and the 5-HT_{2A} receptor (Guillet-Deniau et al., 1997). The Jak/Stat pathway regulates expression of a number of genes including c-Fos, c-Jun and c-Myc (Burysek et al., 2002; Cattaneo et al., 1999), transcription factors which can then stimulate expression of select genes. These transcription factors could impact directly on the expression of proteins in the 5-HT_{2A} receptor signaling system. In A1A1v cells, a cell line that constitutively expresses the 5-HT_{2A} receptor signaling system, 24-h treatment with olanzapine causes desensitization of 5-HT_{2A} receptor signaling and an increase in membrane-associated RGS7 protein that is dependent on activation of the Jak2/Stat3 pathway (Singh et al., 2007). Based on these previous studies in cell culture and as shown in Fig. 1, we hypothesize that chronic treatment with a 5-HT_{2A} receptor antagonist causes alterations in the expression of RGS7 protein and activation of the Jak/Stat pathway in vivo.

2. Methods

2.1. Treatment

Male Sprague–Dawley rats (250–275 g; Harlan Laboratories, Indianapolis, IN) were housed 2 in a cage in an environment controlled for temperature, humidity, and lighting (lights on 7 am–7 pm), food and water were provided ad libitum. Rats were given 7 daily i.p. injections of olanzapine (0.5 mg/kg, 2.0 mg/kg, or 10 mg/kg) or saline. Olanzapine was chosen because it is clinically used in the treatment of schizophrenia, and it is useful in combination with fluoxetine for treatment-resistant depression, bipolar disorder and other mood disorders (Corya et al., 2006; Marek et al., 2003; Tohen et al., 2003). The olanzapine doses were chosen based on previous data suggesting that a single injection of 2 mg/kg will result in peak concentrations in the clinically relevant range and repeated daily injections of 10 mg/kg per day will result in clinically relevant peak and trough concentrations of olanzapine (Kapur et al., 2003). Rats were weighed every other day during the treatment period. On the 8th day, the rats were injected with either 1 mg/kg (−)-1-(2,5-dimethoxy-4-lodophenyl)-2-aminopropane HCl (DOI) or saline s.c. The rats were killed 30 min post injection by guillotine. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and

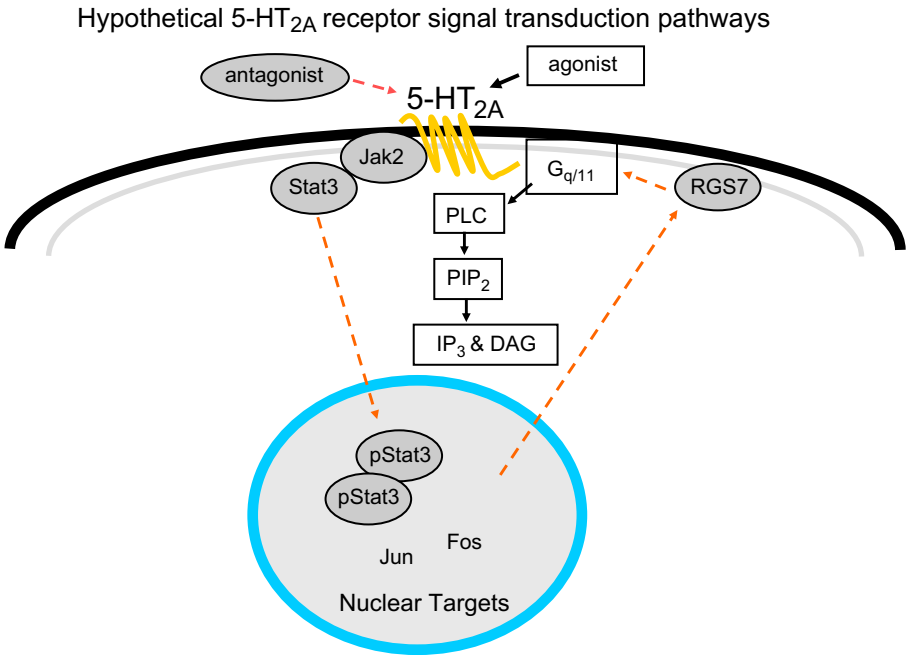

Fig. 1. 5-HT_{2A} receptor agonists cause activation of $G_{\alpha q/11}$ proteins which in turn activate the second messenger enzyme PLC. Chronic treatment with olanzapine causes desensitization of this pathway as measured by either production of inositol phosphate in cells or PLC activity in brain tissue. We hypothesize that 5-HT_{2A} receptor antagonism (induced by olanzapine) activates the Jak2/Stat3 pathway causing phosphorylated Stat3 to dimerize and translocate to the nucleus, stimulate immediate early genes and subsequently increase RGS7 transcription and RGS7 protein levels in the membrane. The increased membrane-associated RGS7 protein can then increase hydrolysis of activated $G_{\alpha q/11}$ and result in desensitization of 5-HT_{2A} receptor signaling.

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