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# Effect of antipsychotic drugs on DISC1 and dysbindin expression in mouse frontal cortex and hippocampus

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**Summary.** Altered expression of Disrupted-In-Schizophrenia-1 (DISC1) and dysbindin (DTNBP1), susceptibility genes for schizophrenia, in schizophrenic brain has been reported; however, the possible effect of antipsychotics on the expression levels of these genes has not yet been studied. We measured the mRNA expression levels of these genes in frontal cortex and hippocampus of mice chronically treated with typical and atypical antipsychotics by a real-time quantitative RT-PCR method. We found that atypical antipsychotics, olanzapine and risperidone, in a clinically relevant dose increased DISC1 expression levels in frontal cortex, while a typical antipsychotic, haloperidol, did not. No significant effect on dysbindin expression levels was observed in either brain region. These data suggest that prior evidence of decreased expression of dysbindin in postmortem brain of schizophrenics is not likely to be a simple artifact of antemortem drug treatment. Our results also suggest a potential role of DISC1 in the therapeutic mechanisms of certain atypical antipsychotics.

**Keywords:** Antipsychotic, DISC1, dysbindin, schizophrenia, gene expression.

## Introduction

Schizophrenia is a common neuropsychiatric disorder affecting 0.5–1% of the general population worldwide. The pathophysiology of schizophrenia is still unclear; however, this disease is highly heritable (Owen et al., 2004). Several genes, e.g. Disrupted-In-Schizophrenia 1 (DISC1), dysbindin, catechol-O-methyltransferase, neuregulin 1, the regulator of G-protein signaling-4, GRM3 and G72 have been proposed as susceptibility genes for schizophrenia (Harrison and Weinberger, 2005).

The DISC1 gene has initially been identified at the breakpoint of a balanced translocation (1;11) (q42.1;q14.3), which segregates with schizophrenia and related psychiatric

disorders in a large Scottish family (Millar et al., 2000). Genetic association and linkage studies have also suggested that the DISC1 gene may be implicated in schizophrenia in independent populations (Ekelund et al., 2001, 2004; Hennah et al., 2003; Hodgkinson et al., 2004; Callicott et al., 2005). The function of DISC1 is still unclear, however, increasing evidence suggests a role in cytoskeletal organization, as DISC1 interacting proteins are associated with the components of microtubule and actin (Millar et al., 2003; Miyoshi et al., 2003; Morris et al., 2003b; Ozeki et al., 2003). Expression analysis of DISC1 using lymphocytes from patients in a balanced translocation family revealed that patients with the breakpoint expressed lower expression of DISC1 compared with controls, suggesting that lower levels of DISC1 might be related to the pathogenesis of schizophrenia (James et al., 2004). Further recent evidence implicates DISC1 in transcription regulation (Sawamura et al., 2005).

A significant association between schizophrenia and genetic variation in dysbindin has been reported in various populations from Ireland, Wales, Germany/Hungary/Israel, Sweden, Bulgaria, United States, China, and Japan (Straub et al., 2002; Schwab et al., 2003; Tang et al., 2003; Van Den Bogaert et al., 2003; van den Oord et al., 2003; Funke et al., 2004; Kirov et al., 2004; Numakawa et al., 2004; Williams et al., 2004). One study, which failed to replicate a positive association based on single SNPs in an Irish population, was subsequently positive using a haplotype strategy (Morris et al., 2003a). Dysbindin is a binding partner of alpha- and beta-dystrobrevins, which are parts of the dystrophin-associated protein complex (Benson et al., 2001), and is a component of the biogenesis of lysosome-related organelles complex 1, which regulates trafficking to lysosome-related organelles (Li et al., 2003). Recently, dysbindin has been reported to play roles in glutamate release and in cell models of neuroprotection, which have also been hypothesized to be related to the pathophysiology of schizophrenia (Numakawa et al., 2004).

Abnormal expression of DISC1 and dysbindin in schizophrenic brain has been reported. The expression ratio of an isoform of DISC1 was increased within the nuclear fraction extracted from orbitofrontal cortex of brains from patients with schizophrenia and also major depression (Sawamura et al., 2005) and the mRNA levels of DISC1 tended to be increased in hippocampus in patients with schizophrenia (Lipska et al., 2004). The expression levels of dysbindin mRNA and protein were reduced in the prefrontal cortex and hippocampus in schizophrenic brain (McClintock et al., 2003; Talbot et al., 2004; Weickert et al., 2004). In studies of schizophrenic postmortem brain, patients have received antipsychotic medication at various times in their lives, including in most cases around the time of death, while control subjects do not. Thus, possible effects of antipsychotics on gene expression are an important potential confounder when interpreting results of postmortem tissue studies of schizophrenic cases. Here, we examined for a possible effect of chronic administration of typical and atypical antipsychotics on the mRNA expression levels of DISC1 and dysbindin in mouse frontal cortex and hippocampus.

## Materials and methods

### *Drug preparation*

Haloperidol, risperidone and clozapine were purchased from Sigma-Aldrich (Tokyo, Japan). Olanzapine was a gift from Eli Lilly and Company Lilly Corporate Center (Greenfield, IN). Haloperidol was dissolved in glacial acetic acid solution, diluted with saline up to 1 ml with adjustment to pH 5.5 with 1 N sodium hydroxide, and brought to a final concentration of 0.005 or 0.1 mg/ml. Clozapine was dissolved in glacial acetic acid solution, diluted with saline up to 1 ml with adjustment to pH 5.5 with 8 N sodium hydroxide, and brought to a final concentration of 0.05 or 1 mg/ml. Olanzapine and risperidone were dissolved in 1 N acetic acid solution, diluted

with saline up to 1 ml with adjustment to pH 5.5 with 1 N sodium hydroxide, and brought to a final concentration of 0.004 or 1 mg/ml (olanzapine) and 0.0025 or 0.075 mg/ml (risperidone), respectively.

### *Animals and drug treatment*

Male C57BL/6J mice (CLEA, Japan) weighing 20–25 g received once-daily injections intraperitoneally (i.p.) for 21 days with haloperidol (clinical dose: 0.05 mg/kg; high dose: 1 mg/kg), olanzapine (clinical dose: 0.04 mg/kg; high dose: 10 mg/kg), risperidone (clinical dose: 0.025 mg/kg; high dose: 0.75 mg/kg), clozapine (clinical dose: 0.5 mg/kg; high dose: 10 mg/kg), or vehicle (0.1 N acetic acid in saline). This dose regimen was chosen to simulate the therapeutic range of doses given to patients (Kapur et al., 2000), and was shown to be effective in several behavioral and biochemical studies (Lipska et al., 2001; Parikh et al., 2004). Haloperidol is a typical (conventional) antipsychotic, whereas the others are termed atypical antipsychotics, which are associated with fewer motor side effects and possibly greater efficacy. Animals were sacrificed 20 hr after the final injection. Brain regions were removed, frozen in liquid nitrogen, and stored at −80°C. The experimental protocols were approved by the Ethics Review Committee for Animal Experimentation of the National Institute of Neuroscience, Japan.

### *RNA extraction, DNAse treatment and reverse transcriptase reaction*

Tissues from frontal cortex or hippocampus were homogenized in 4 mol/L guanidinium isothiocyanate (containing 25 nmol/L sodium citrate, pH 7.5, and 1% 2-mercaptoethanol), and total RNA was isolated by a standard phenol-chloroform extraction. The yield of total RNA determined by the absorbance at 260 nm and the quality of total RNA was also analyzed using agarose gel electrophoresis.

Total RNA was treated with DNase for removal of contaminating genomic DNA using DNase Treatment & Removal Reagents (Ambion, Austin, TX), according to the manufacturer's protocol. Total RNA (3.3 μg) treated with DNase was used in 50 μl of reverse transcriptase reaction to synthesize cDNA, by using a SuperScriptII First-Strand Synthesis System for RT-PCR (Invitrogen, Carlsbad, CA), according to the manufacturer's protocol. Briefly, total RNA (3.3 μg) was denatured with 1 mM of dNTP and 6 ng/μl of random primers at 65°C for 5 min. After addition of RT buffer, dithiothreitol (10 mM in final concentration), RNAsin Plus RNase Inhibitor (40 units) and SuperScriptII RT (200 units), the reaction mixture was incubated at 25°C for 10 min, at 42°C for 40 min, and at 70°C for 15 min. RNAse H (2 units) was added to the reaction mixture and then incubated at 37°C for 20 min.

### *Real-time quantitative PCR*

The TaqMan® Endogenous Controls (Applied Biosystems, Foster City, CA) were used for measurements of house keeping genes, β-actin (Mm00607939_s1) and GAPDH (Mm99999915_q1). TaqMan® Gene Expression Assays (Applied Biosystems) were used for DISC1 (Mm00533313_m1) and dysbindin (Mm00458743_m1) genes. Both TaqMan assay kits included optimized concentrations of primers and probes to detect the target gene expression. The levels of mRNA expression of these genes were measured by a real-time quantitative RT-PCR using an ABI Prism 7900 sequence detection system with 384-well format (Applied Biosystems), described previously (Hashimoto et al., 2004). Briefly, each 20 μl PCR reaction mixture contained 6 μl of cDNA, 0.5 μl of TaqMan assay kit and 10 μl of TaqMan Universal PCR Mastermix (Applied Biosystems). PCR cycling conditions were: 50°C for 2 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. PCR data were obtained with the Sequence Detector Software (SDS version 2.1, Applied Biosystems) and quantified by a standard curve method. Standard curves were prepared using serial dilutions (1:4) of pooled cDNA from total RNA derived from whole brain of three mice.

### *Statistical analysis*

An analysis of variance (ANOVA) was used to compare gene expression levels between drug treatment groups with SPSS 11.0J for Windows (SPSS Japan Inc, Tokyo, Japan). Bonferroni post hoc comparisons were performed when applicable. Statistical significance was defined at $p < 0.05$.

## Results

The expression levels of the two standard ''housekeeping'' genes, β-actin and GAPDH in frontal cortex and hippocampus of control mice and mice treated with typical or atypical antipsychotics for three weeks in clinical or high dose are shown in Table 1. The expression levels of both genes in frontal cortex and hippocampus were not significantly influenced by drug treatments at clinical dosing (all p values >0.4, ANOVA), however, there was a significant drug treatment effect on expression of the two house keeping genes

**Table 1.** Expression analysis of house keeping genes in frontal cortex and hippocampus in clinical and high dose

| Drugs | | Clinical dose | | High dose | | | |
|---|---|---|---|---|---|---|---|
| | | Frontal cortex (n) | Hippocampus (n) | Frontal cortex (n) | *p* value | Hippocampus (n) | *p* value |
| VEH | β-actin | 100.0 ± 36.4 (19) | 100.0 ± 33.1 (19) | 100.0 ± 36.4 (19) | | 100.0 ± 33.1 (19) | |
| | GAPDH | 100.0 ± 22.8 (19) | 100.0 ± 26.6 (19) | 100.0 ± 22.8 (19) | | 100.0 ± 26.6 (19) | |
| HPD | β-actin | 105.4 ± 33.0 (10) | 91.5 ± 16.7 (10) | 72.2 ± 22.6 (12) | NS | 102.8 ± 39.3 (12) | NS |
| | GAPDH | 95.8 ± 15.9 (10) | 96.7 ± 24.5 (10) | 86.1 ± 15.5 (12) | NS | 112.8 ± 29.7 (12) | NS |
| OZP | β-actin | 139.4 ± 34.8 (10) | 90.3 ± 40.4 (10) | 67.4 ± 19.4 (12) | 0.023 | 65.8 ± 22.1 (12) | 0.041 |
| | GAPDH | 118.3 ± 22.8 (10) | 89.4 ± 26.3 (10) | 73.5 ± 11.3 (12) | 0.002 | 77.5 ± 19.9 (12) | NS |
| RPD | β-actin | 99.2 ± 32.7 (10) | 83.4 ± 16.8 (10) | 75.6 ± 24.8 (11) | NS | 75.0 ± 33.1 (11) | NS |
| | GAPDH | 92.3 ± 24.9 (10) | 93.0 ± 30.4 (10) | 88.0 ± 20.9 (11) | NS | 94.7 ± 34.9 (11) | NS |
| CZP | β-actin | 105.7 ± 40.9 (9) | 88.1 ± 27.3 (9) | 67.2 ± 25.1 (11) | 0.027 | 84.5 ± 22.8 (12) | NS |
| | GAPDH | 93.1 ± 36.3 (9) | 85.6 ± 20.3 (9) | 72.9 ± 14.0 (11) | 0.002 | 90.3 ± 22.7 (12) | NS |

*VEH* vehicle, *HPD* haloperidol, *OZP* olanzapine, *RPD* risperidone, *CZP* clozapine, *NS* not significant, *n* number of animals used. Data are the means ± SD. Post hoc *p* values compared with VEH are shown

at high dosing (frontal cortex: β-actin, $F_{4, 60} = 3.97$, $p = 0.006$, GAPDH, $F_{4, 60} = 5.73$, $p = 0.001$; hippocampus: β-actin, $F_{4, 61} = 3.42$, $p = 0.014$, GAPDH, $F_{4, 61} = 2.79$, $p = 0.034$). Post hoc analysis revealed that the expression levels of β-actin and/or GAPDH were significantly decreased in mice received clozapine or olanzapine in high dose. Body weight loss or lower level of body weight gain after three weeks of drug administration was also observed in clozapine or olanzapine treated mice in high dose compared with control mice (body weights change ± standard deviation for clozapine: $-0.73 \pm 0.51$ g, $p = 0.00005$; olanzapine: $0.67 \pm 0.81$ g, $p = 0.083$, control: $1.57 \pm 1.62$ g), while no significant difference was observed at the clinical dose (clozapine: $2.5 \pm 1.02$ g, $p = 0.13$; olanzapine: $2.31 \pm 0.88$ g, $p = 0.19$; control: $1.57 \pm 1.62$ g). These results suggest that olanzapine and clozapine treatment in high dose might affect the general health of mice, which could result in the altered expression levels of house keeping genes. Thus, we focused on possible effects on the gene expression levels of DISC1 and dysbindin at the clinical dose only.

The expression levels of DISC1 mRNA normalized by β-actin and GAPDH (to reduce effects of possible mRNA degradation not detectable by electrophoresis and possible variations in RT efficiency) in frontal cortex of mice administrated with a typical antipsychotic (haloperidol) or atypical antipsychotics (olanzapine, risperidone, clozapine) at the clinical dose are shown in Fig. 1. Analysis of the DISC1 expression demonstrated significant effects of drug treatments (normalized by β-actin, $F_{4, 53} = 6.41$, $p < 0.001$, or GAPDH, $F_{4, 53} = 5.25$, $p = 0.001$). Post hoc analysis revealed that DISC1 expression levels were increased by treatments with atypical antipsychotics, olanzapine (normalized by β-actin: 36%, $p = 0.0029$; or GAPDH: 64%, $p = 0.016$) and risperidone (normalized by β-actin: 39%, $p = 0.0077$; or GAPDH: 55%, $p = 0.0031$) compared with the control group. No significant difference of DISC1 expression levels was observed after treatment with the typical antipsychotic (haloperidol). Elevated expression levels of the DISC1 gene normalized by β-actin were also found in olanzapine (36%, $p = 0.013$) and risperidone (39%, $p = 0.028$) treatment groups compared with haloperidol. Similar trends were obtained after normalization with GAPDH (olanzapine: 45%, $p = 0.095$; risperidone: 37%, $p = 0.30$). Treatment with clozapine tended to increase the expression levels of the DISC1 gene compared with control group, although they did not reach statistical significance.

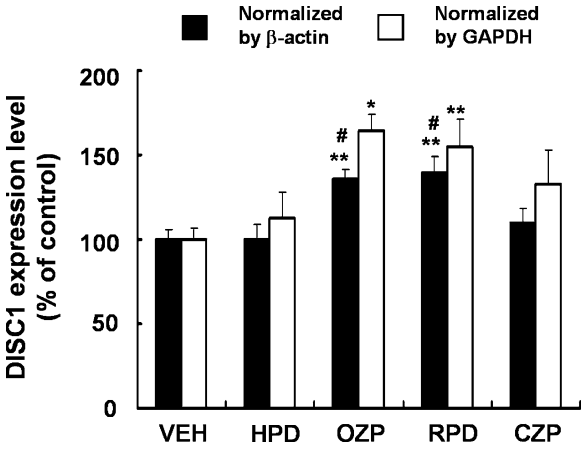


**Fig. 1.** Relative expression levels of DISC1 in frontal cortex in clinical dose. DISC1 mRNA expression levels normalized by β-actin or GAPDH in control mice (treated with vehicle: VEH) and mice treated with haloperidol (HPD), olanzapine (OZP) risperidone (RPD), or clozapine (CZP) are shown. Expression levels were calculated by comparison to percentage of average of those of control mice. Data are the means ± SEM from 19 control mice or mice treated with HPD (n = 10), OZP (n = 10), RPD (n = 10) or CZP (n = 9). $^{*}p < 0.05$, $^{**}p < 0.01$, compared with the control group. $\#p < 0.05$, compared with the haloperidol treated group

The expression levels of DISC1 mRNA normalized by β-actin and GAPDH in hippocampus of mice administrated with a typical antipsychotic or atypical antipsychotics at the clinical dose are shown in Fig. 2. Analysis of the DISC1 expression in hippocampus

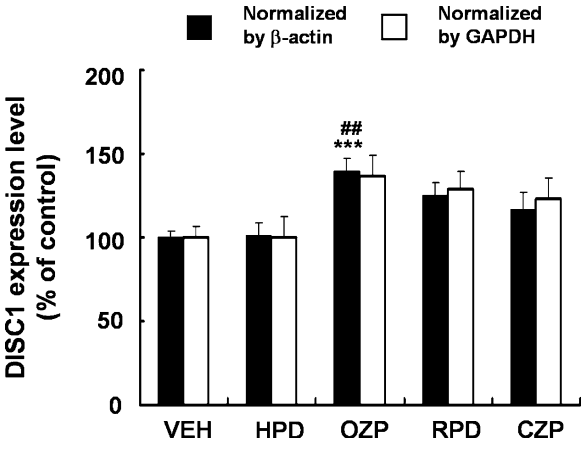


**Fig. 2.** Relative expression levels of DISC1 in hippocampus in clinical dose. DISC1 mRNA expression levels normalized by β-actin or GAPDH in control mice (treated with vehicle: VEH) and mice treated with haloperidol (HPD), olanzapine (OZP) risperidone (RPD), or clozapine (CZP) are shown. Expression levels were calculated by comparison to percentage of average of those of control mice. Data are the means ± SEM from 19 control mice or mice treated with HPD (n = 10), OZP (n = 10), RPD (n = 10) or CZP (n = 9). $^{***}p < 0.001$, compared with the control group. $\#\#p < 0.01$, compared with the haloperidol treated group

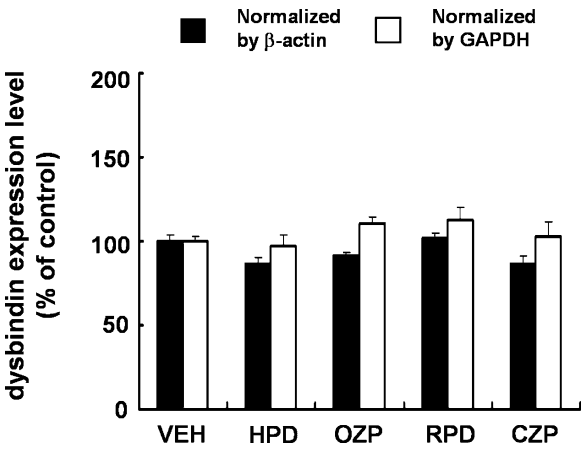


**Fig. 3.** Relative expression levels of dysbindin in frontal cortex in clinical dose. Dysbindin mRNA expression levels normalized by β-actin or GAPDH in control mice (treated with vehicle: VEH) and mice treated with haloperidol (HPD), olanzapine (OZP) risperidone (RPD), or clozapine (CZP) are shown. Expression levels were calculated by comparison to percentage of average of those of control mice. Data are the means ± SEM from 19 control mice or mice treated with HPD (n = 10), OZP (n = 10), RPD (n = 10) or CZP (n = 9)

demonstrated significant effects of drug treatments (normalized by β-actin, $F_{4, 53} = 6.09$, $p < 0.001$, or GAPDH, $F_{4, 53} = 2.82$, $p = 0.034$). In post hoc analysis, DISC1 expression levels normalized by β-actin were significantly increased by the atypical antipsychotic, olanzapine, compared with control (39%, $p = 0.0006$) or haloperidol (29%, $p = 0.0054$) and similar trend was observed in risperidone compared with control (25%, $p = 0.079$). On the other hand, a slight increase of DISC1 expression was also found when normalizing by GAPDH (olanzapine vs control: 37%, $p = 0.094$; olanzapine vs haloperidol: 29%, $p = 0.23$; risperidone vs control: 29%, $p = 0.39$), which did not reach statistical significance. No effect of haloperidol or clozapine treatment was found in either normalization. These findings suggest that the mRNA expression levels of the DISC1 gene are increased by the chronic administration of some atypical antipsychotics in frontal cortex and possibly in hippocampus.

The expression levels of dysbindin mRNA normalized by β-actin and GAPDH in frontal cortex and hippocampus of mice administered treatment with a typical antipsychotic or atypical antipsychotics at the clinical dose are shown in Figs. 3 and 4. Dysbindin gene expression normalized by either β-actin or GAPDH in frontal cortex or hippocampus did not significantly differ between the treatment groups (frontal cortex: GAPDH, $F_{4, 53} = 1.45$, $p = 0.23$; hippocampus: β-actin, $F_{4, 53} = 0.64$, $p = 0.64$, GAPDH, $F_{4, 53} = 0.46$, $p = 0.77$), except for that in frontal cortex normalized by β-actin ($F_{4, 53} = 3.68$, $p = 0.01$). However, post hoc analysis demonstrated no significant difference in dysbindin expression in frontal cortex normalized by β-actin in any of the drug treatments, although there were trends towards slightly decreased expression of dysbindin in mice

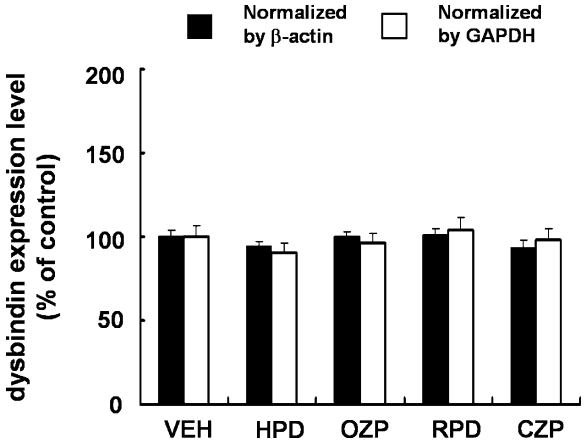


**Fig. 4.** Relative expression levels of dysbindin in hippocampus in clinical dose. Dysbindin mRNA expression levels normalized by β-actin or GAPDH in control mice (treated with vehicle: VEH) and mice treated with haloperidol (HPD), olanzapine (OZP) risperidone (RPD), or clozapine (CZP) are shown. Expression levels were calculated by comparison to percentage of average of those of control mice. Data are the means ± SEM from 19 control mice or mice treated with HPD ($n = 10$), OZP ($n = 10$), RPD ($n = 10$) or CZP ($n = 9$)

treated with haloperidol, compared with control (14%, $p = 0.074$) and in mice treated with risperidone (16%, $p = 0.094$). These data suggest that administration of typical and atypical antipsychotics do not have a consistent influence on mRNA expression levels of the dysbindin gene in frontal cortex or in hippocampus.

## Discussion

In this study, we have measured mRNA expression levels of two susceptibility genes for schizophrenia, DISC1 and dysbindin, in frontal cortex and hippocampus using a real-time quantitative RT-PCR in mice treated chronically with typical or atypical antipsychotics. We found preliminary evidence that the expression levels of DISC1 may be altered by treatment with the atypical agents in frontal cortex and possibly in hippocampus and that the expression levels of dysbindin may not be changed under these conditions. Upregulation of DISC1 mRNA in frontal cortex by olanzapine and risperidone was observed in both normalizations by β-actin and GAPDH, however, that in hippocampus by olanzapine was found only in normalization by β-actin. As DISC1 has been shown to interact with actin (Miyoshi et al., 2003), it is possible that the DISC1 mRNA expression level normalized by β-actin in hippocampus may be somehow affected by the interaction. Upregulation of DISC1 mRNA in hippocampus by atypical antipsychotics appears to be marginal while that in frontal cortex is more apparent. As DISC1 expression is dominant in hippocampus compared with frontal cortex (Miyoshi et al., 2003), there is a possibility that this differential expression of DISC1 might affect the degree of the upregulation of DISC1 mRNA by the atypical antipsychotics.

Specifically, there was an increase of DISC1 expression levels after treatment with olanzapine and risperidone and possibly with clozapine in a simulated clinical dose in frontal cortex. As consistent results were obtained from normalization of the DISC1 expression by two house keeping genes, our findings would seem to be robust at least in comparison to results that might have been based on using only one control gene. However, it should be noted that there were some effects of antipsychotics on housekeeping gene expression, though largely nonsignificant. It is conceivable that some of the effect on our measures of DISC1 expression could be exaggerated by these effects on our control genes, as significant effects of drug treatments on the raw expression levels of DISC1 (non-normalized) were not observed in either frontal cortex or hippocampus (data not shown). Our data raise the possibility that DISC1 may be involved in the treatment of schizophrenia. However, as our study did not include the measurement of DISC1 proteins, or expression in other brain regions, or of treatment with other psychotropic drugs, further work is necessary to clarify whether

changes in DISC1 mRNA impact on protein expression and are specific for brain regions and psychotropic drugs. It also should be noted that we measured expression only of the common transcript for both of these genes. It is not currently known whether schizophrenia involves alternate processing of these genes into disease related transcripts or isoforms and we cannot rule out that treatment may impact on variable splicing or processing of these genes.

A balanced translocation in the DISC1 gene segregates with schizophrenia and other major psychiatric illnesses in a Scottish family (Millar et al., 2000). However, little is known about how the translocation affects the expression and/or function of the DISC1 gene. DISC1 protein expression in lymphoblasts derived from the family member with the translocation was observed to be decreased but the mutant truncated form of DISC1, which should be produced by the translocation, was not found (James et al., 2004). It is unknown whether the expression of DISC1 in brains of the family members is altered or not, however, this observation in peripheral cells suggested that the translocation might decrease the expression of DISC1. Alternatively, mutant truncated form of DISC1, which has been shown to play a role in inhibiting neurite outgrowth (Ozeki et al., 2003), might down-regulate the DISC1 protein expression and/or function. These findings suggest that reduced expression of DISC1 in brain might be expected in schizophrenic brain if DISC1 is involved in the pathogenesis of schizophrenia. On the other hand, gross expression levels of DISC1 protein have not been found to be changed in frontal cortex in patients with schizophrenia (Sawamura et al., 2005) and expression levels of DISC1 mRNA tended to be increased in hippocampus of schizophrenia patients (Lipska et al., 2004). Our data suggest that increased expression of DISC1 mRNA may be, at least in part, related to treatment with some atypical antipsychotics.

Evidence that dysbindin is associated with schizophrenia is now quite strong, although no functional mutation in dysbindin gene has yet been identified. Recent postmortem studies have found decreased expression of dysbindin mRNA and protein in hippocampus and frontal cortex in schizophrenic patients (McClintock et al., 2003; Talbot et al., 2004; Weickert et al., 2004). In contrast to our data with DISC1, we found no consistent pattern of altered dysbindin expression in hippocampus and frontal cortex following antipsychotic treatment.

Knowledge about protein functions of DISC1 and dysbindin is insufficient, however, we discuss a possibility how these genes affect the mechanisms of schizophrenia. As DISC1 has a prominent role in the neurite extension and its expression is developmentally regulated (Ozeki et al., 2003), upregulation of DISC1 could support the maturation of dendritic spine, which is believed to be affected in schizophrenia. As dysbindin promotes glutamate release in neuronal culture (Numakawa et al., 2004), reduced expression of dysbindin in schizophrenic brain could be relevant to glutamatergic dysfunction, which has been implicated in the pathophysiology of schizophrenia.

In summary, our findings offer preliminary evidence that altered expression of DISC1 may be caused by certain antipsychotic drugs, suggesting a role for DISC1 in therapeutic actions of these drugs. Additional studies are warranted to examine DISC1 and dysbindin expression, including western blotting analysis, in situ hybridization, immunohistochemistry, and the effect of other psychotropic drugs.

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