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ORIGINAL INVESTIGATION

Effect of aripiprazole, risperidone, and olanzapine on the acoustic startle response in Japanese chronic schizophrenia

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Abstract
Background Studies have also shown that differences in the kind of the antipsychotics influenced disruption of the sensorimotor gating system, including prepulse inhibition (PPI), acoustic startle reflex (ASR), and habituation (HAB). We investigated the influence on startle response in chronic schizophrenia in 20 patients with schizophrenia taking risperidone, 21 patients with schizophrenia taking olanzapine, and 20 patients with schizophrenia taking aripiprazole.
Method The patients who participated in this study were on maintenance therapy with only one antipsychotic drug for 4 months. We performed the test for the association between all PPI measures (ASR, HAB, and PPI at prepulse sound pressure intensities of 82, 86, and 90 dB) and each the risperidene, olanzapine, and aripiprazole groups, with analysis of covariance (ANCOVA; using age, duration of illness, and daily dose of the antipsychotic as covariates). Also, when significant difference was detected in ANCOVA, the differences of PPI measures between every pairs of two drug groups were tested as a post hoc analysis with the use of *t* test and Bonferroni's correction of multiple tests.
Result We found that PPI90 showed significant differences with ANCOVA among patients with schizophrenia taking each of the antipsychotics. When we performed a post hoc analysis for PPI90, the value was higher in the aripiprazole group than in the olanzapine group and higher in the risperidone group than in the olanzapine group.
Conclusion Aripiprazole and risperidone may improve PPI90. ASR, HAB, PPI82, and PPI86 were no different among the Japanese schizophrenic patient groups with different antipsychotics.

Keywords Acoustic startle response · Risperidone · Aripiprazole · Olanzapine · Schizophrenia · Prepulse inhibition · Antipsychotic

Abbreviations

PPI	Prepulse inhibition
ASR	Acoustic startle reflex
HAB	Habituation
OLZ	Olazapine
RIS	Risperidone
HPD	Haloperidol
ARP	Aripiprazole
SD	Standard deviation
SCID-1	Structured Clinical Interview for DSM-IV disorders
LI	Lead interval
PA trial	Pulse alone trials
PP trials	Trials of pulse with prepulse
ANOVA	Analysis of variance

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ANCOVA	Analysis of covariance
5-HT1A receptor	Serotonin 1A receptor
5-HT1B receptor	Serotonin 1B receptor
α2c receptor	Adrenergic alpha2c receptor
MDMA	Methylenedioxy-substituted phenalkylamines 3,4-methylenedioxy-*N*-methylamphetamine
M5 receptors	Muscarinic acetylcholine 5 receptors

Introduction

Disruption of the sensorimotor gating system, including prepulse inhibition (PPI) deficit, the acoustic startle reflex (ASR), and habituation (HAB), is suggested to be one of involved in the pathophysiology of schizophrenia (Braff et al. 1992; Kunugi et al. 2007; Takahashi et al. 2008; Walters and Owen 2007). These abnormalities are also considered to be endophenotypes for schizophrenia (Braff et al. 1992; Kunugi et al. 2007; Takahashi et al. 2008; Walters and Owen 2007). Recently, we detected significant differences in ASR, HAB, and each PPI (82, 86, and 90 dB) between patients with schizophrenia and controls (Moriwaki et al. 2009). Several investigations have reported that the ASR and PPI are influenced by factors such as gender and smoking state (Kumari et al. 1996, 1997, 2004; Swerdlow et al. 1999). However, we found no correlation between gender or current smoking state and ASR, HAB, or any PPI in a multiple regression analysis (Moriwaki et al. 2009).

It has also been reported that several measures of the startle response were influenced by the kind of antipsychotic. Wynn and colleagues also reported that olazapine (OLZ) improved the startle acoustic response significantly compared with risperidone (RIS) and haloperidol (HPD) in people with schizophrenia (Wynn et al. 2007). The antipsychotic aripiprazole (ARP) is known to be a dopamine system stabilizer, the pharmacological mechanism of which is a unique partial agonistic action on dopamine 2 receptors (Burris et al. 2002; Jordan et al. 2002). To our knowledge, there is no investigation on the influence ARP in the startle response in people with schizophrenia. Therefore, we investigated whether some antipsychotics, including ARP, RIS, and OLZ, influenced the startle response in chronic schizophrenia.

Materials and methods

Subjects

One hundred forty-one patients with schizophrenia (91 males and 50 females: mean age standard deviation (SD) 49.8±15.6 years) were recruited. This study increased 26 patients compared with our previous study (Moriwaki et al. 2009). However, because 17 patients were nonresponders, these patients excluded the further analysis. Detailed information about exclusion criteria can be seen in the paper of Takahashi et al. (2008). Among 124 patients, 71 patients were taken monotherapy antipsychotics. Also, 53 patients were taken polytherapy antipsychotics. All subjects were unrelated to each other, ethnically Japanese, and lived in the central area of Japan. The patients were diagnosed according to DSM-IV criteria with the consensus of at least two experienced psychiatrists on the basis of a structured interview using the Structured Clinical Interview for DSM-IV disorders (SCID-1) and a review of medical records. All met the following inclusion criteria: (1) age 25 to 70 years, (2) no systemic or neurologic disease, (3) no electroconvulsive therapy, (4) no history of head trauma, (5) no lifetime history of substance dependence or history of substance abuse within 3 months, and (6) use of only one antipsychotic drug therapy for 4 months. All patients were hospitalized at the time of measurement. The study was described to subjects, and written informed consent was obtained from each. This study was approved by the ethics committees at Fujita Health University School of Medicine and Okehazama Hospital.

Startle response measurement

Apparatus and stimuli

We measured startle response using a commercial computerized human startle response monitoring system (Startle Eyeblink Reflex Analysis System Map1155SYS, Nihonsanteku Co., Osaka, Japan). Startle eyeblink electromyographic responses were recorded from the left orbicularis oculi muscle with two Ag/AgCl disposable electrodes (sensor area 15 mm^2), filled with wet gel. The first electrode (Blue Sensor N-00-S, Ambu, Ballerup, Denmark) was positioned approximately 1 cm directly below the pupil of the left eye and low enough to not touch the lower eyelid, while the second electrode (Blue Sensor M-00-S, Ambu, Ballerup, Denmark) was placed laterally and slightly superior to the first one, with the centers of the electrodes separated by approximately 2 cm. The impedance between the two electrodes was measured and deemed acceptable if below 5 kΩ. The impedance was measured with an electrode impedance meter (MaP811, Nihonsanteku Co., Osaka, Japan) at a measurement frequency of 30 Hz. The ground electrode (Blue Sensor M-00-S) was placed on the left angle of the mandible. We used a method same as in the study of Takahashi and colleagues (Takahashi et al. 2008). Detailed information can be seen in their paper.

The stimulus sequence, procedure, and response scoring and data reduction

Measurements were made with startle paradigm constructed of three blocks with continuous background white noise of 70 dB SPL. Pulse stimuli consisted of broadband white noises with an instantaneous rise/fall time lasting for 40 ms and presented at 115 dB SPL. Prepulse stimuli were also broadband white noises with an instantaneous rise/fall time lasting for 20 ms, presented at three different intensities (82, 86, and 90 dB SPL). The LI (from prepulse onset to pulse onset) in our study was set at 120 ms. In block 1, the startle response for pulse alone trials (PA trial) was recorded six times. Block 2 consisted of PA trials or trials of pulse with prepulse at three intensities (PP trials), performed eight times for each condition. Block 3 was the same as block 1, to measure habituation. All trials were presented in a fixed pseudorandom order, separated by inter-trial intervals of 15–25 s (20 s on average). The startle paradigm consisted of a total of 44 trials. Together with 5 min acclimation to the background noise, the session lasted approximately 20 min. We used the same method as Takahashi and colleagues (2008). Detailed information can be seen in their paper.

Statistical analysis

The numbers of patients, who took monotherapy antipsychotics, were 20 in the RIS group, 21 in the OLZ group, 20 in the ARP group, four in the quetiapine group, one in the perospirone group, two in the blonanserin group, two in the HPD group, and one in the timiperone group. Because our samples of quetiapine, perospirone, blonanserin, HPD, and timiperone group were small, we included only the RIS, OLZ, and ARP groups in this study. All demographic data were analyzed by one-way analysis of variance (ANOVA). As described in the “Results” section, the mean age of ARP group was youngest among three drug groups; meanwhile, the duration of illness was shortest, and the daily dose of the antipsychotic was the largest in ARP group. So we performed analyses of covariance (ANCOVA) for comparing the PPI measures among the three drug groups, using the above three parameters as covariates to adjust possible confounding. When significant difference was detected in ANCOVA, the differences of PPI measures between every pairs of two drug groups were tested as a post hoc analysis with the use of *t* test and Bonferroni’s correction of multiple tests. The significance level for all statistical tests was 0.05.

All statistical analyses were performed using SPSS (SPSS 12.0, SPSS Japan Inc., Tokyo, Japan).

Results

The mean age of ARP group was youngest among three drug groups; meanwhile, the duration of illness was shortest, and the daily dose of the antipsychotic was the largest in ARP group. Although one-way ANOVA did not show significant difference as to these three parameters among the three drug groups (Table 1), we conducted ANCOVA for comparing the PPI measures among three drug groups, using the above three parameters as covariates to adjust possible confounding. We found that PPI90 were significantly different among the ARP, RIS, and OLZ groups with the use of ANCOVA (P=0.0320; Table 2). We then performed a post hoc analysis of PPI90 and found that the ARP group had higher PPI90 than the OLZ group (P=0.0178; Fig. 1). Also, PPI90 was higher in the RIS group than in the OLZ groups (P=0.0368; Fig. 1).

Discussion

We first investigated whether ARP influenced the startle response. Also, because the participating patients took only one antipsychotic, we considered the effect of each antipsychotic on acoustic startle response in people with

Table 1 Schizophrenic patients’ demographics and disposition

	Aripiprazole	Risperidone	Olanzapine	*P* value
N	20	20	21	
Sex (males/females)	14/6	10/10	13/8	0.231
Age, years (mean±SD)	46.7±17.1	56.9±16.8	51.0±13.9	0.140
Current smoker/non-smoker, n (%)	8 (40.0%)	7 (47.6%)	10 (35.0%)	0.709
Clinical diagnosis, n (Dis/Res/Par)	2/14/4	1/15/4	0/17/4	0.551
Duration of illness (day, mean ± SD)	8,070±547	10,500±435	9,790±391	0.235
PANSS total score	84.7±20.6	76.3±19.5	76.3±19.5	0.220
Antipsychotics (mg/day)[a]	626±119	505±188	599±245	0.156
Anxiolytics/hypnoticse, *n* (%) (mg/day)[b]	10.3±12.2	12.1±10.5	7.56±6.46	0.337

Dis disorganized type, *Res* residual type, *Par* paranoid type

[a] Chlorpromazine-equivalent

[b] Diazepam-equivalent

Table 2 ANCOVA of startle measure with three antipsychotics groups

Startle measure	Aripiprazole	Risperidone	Olanzapine	*P* value[a]
ASR (μV, mean ± SD)	162±160	74.9±72.3	70.3±30.1	0.108
HAB (%, mean ± SD)	23.3±27.1	24.0±28.3	29.6±25.6	0.103
PPI82 (%, mean ± SD)	32.0±25.7	18.2±16.9	22.6±17.5	0.171
PPI86 (%, mean ± SD)	41.6±25.7	29.7±24.0	23.7±16.0	0.0685
PPI90 (%, mean ± SD)	39.9±31.1	34.9±22.9	21.1±15.9	**0.0320**

Bold represents significant *P* value

ASR acoustic startle reflex, *HAB* habituation, *PPI* prepulse inhibition

[a] Calculated by ANCOVA. *P* values were obtained by ANCOVA using age, duration of illness, and daily antipsychotic dose

schizophrenia directly. In this study, the ARP group had higher scores than the OLZ group in PPI90. Also, the RIS group showed significant difference than the OLZ group in PPI90. We found that PPI86 showed marginal difference among RIS, OLZ, and ARP groups with the use of ANCOVA ($P=0.0685$). When we performed a post hoc analysis for PPI86, the value was higher in the ARP group than in the OLZ groups ($P=0.0634$). From this result, we considered that ARP and RIS may improve abnormalities in PPI. We found large differences in the pharmacological profiles of ARP, RIS, and OLZ as follows: first, ARP has stronger affinity with the serotonin 1A (5-HT1A) receptor than RIS and OLZ (Burris et al. 2002; Jordan et al. 2002; Roth et al. 2004). Gogos and colleagues reported that the activation of 5-HT1A receptors increased PPI (Gogos et al. 2008). Also, RIS has stronger affinity with the serotonin 1B (5-HT1B) receptor, serotonin 7 receptor, adrenergic alpha2c (α2c) receptor, adrenergic alpha1a receptor, and adrenergic alpha1b receptors than ARP and OLZ (Roth et al. 2004). Dulawa and colleagues reported that a5-HT1B receptors have relation with ASR, HAB, and PPI in mice (Dulawa et al. 1997, 1998). RU24969, which is 5-HT1A/1B agonist, reduced PPI in WT mice (Shanahan et al. 2009). Dulawa and colleagues reported that the methylenedioxy-substituted phenalkylamines 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) increase PPI in 5-HT1B knockout mice, but not WT mice (Dulawa et al. 2000). These authors suggested that the activation of 5-HT1B receptors by 5-HT decreases PPI (Dulawa et al. 2000). Also, the adrenergic α2c receptor knockout mice showed increased ASR reduced PPI (Sallinen et al. 1998). On the other hand, OLZ has stronger affinity with serotonin 6 receptor, hisitamine 1 receptor, and muscarinic acetylcholine 5 (M5) receptors than RIS and ARP (Roth et al. 2004). Several animal studies using the M5 receptor knockout mice have shown significantly decreased PPI compared to wild-type (Thomsen et al. 2007); however, results have been rather inconsistent (Wang et al. 2004). Second, the antipsychotic aripiprazole is known to be a dopamine system stabilizer, the pharmacological mechanism of which is a unique partial agonistic action on dopamine 2 receptors. Several animal studies using mice reported that ARP restored the abnormalities in the PPI induced by apomorphine (Auclair et al. 2006; Nakai et al. 2008; Nordquist et al. 2008). These mechanisms may be involved in the different effects seen among the antipsychotic groups. However, this has, in seeming contrast to findings by Wynn and colleagues (2007), who reported that OLZ improved the startle acoustic response significantly, compared with RIS in people with schizophrenia. We consider that a replication study using larger samples or samples of other populations will be required for conclusive results.

Our previous study reported significant differences in ASR, HAB, and each PPI (82, 86, and 90 dB) between 115 patients with schizophrenia and 111 controls in multiple regression analysis (there were 15 nonresponders in the patient group and four in the control group; therefore, we performed the analysis of startle measure with 100 patients and 107 controls) (Moriwaki et al. 2009). When all PPI measures (except HAB) in the ARP group were compared with our 107 healthy control subjects with the use of ANCOVA (using age and sex as covariates), there was no statistical difference between the ARP group and controls

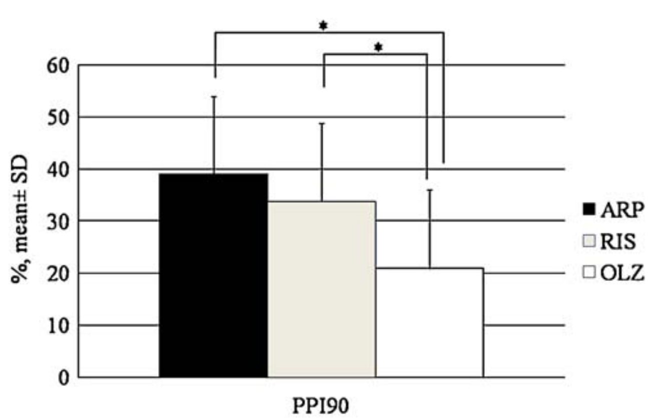

Fig. 1 Bonferroni's *post hoc* analysis of PPI90 in three antipsychotic groups $*P<0.05$, (μV, mean ± SD). ARP group=39.9±31.1, RIS group=33.7±22.9, and OLZ group=21.0±17.9

(detailed information about startle response on controls can be seen in our previous paper and Supplementary Table 1; P_{ASR}=0.686, P_{PPI82}=0.903, P_{PPI86}=0.703, and P_{PPI90}= 0.141) (Moriwaki et al. 2009). In addition, when all PPI measures (except HAB) in the RIS group were compared with our 107 healthy control subjects with the use of ANCOVA (using age and sex as covariates), there was no statistical difference between the RIS group and controls (Supplementary Table 1; P_{ASR}=0.485, P_{PPI82}=0.267, P_{PPI86}=0.900, and P_{PPI90}=0.331) (Moriwaki et al. 2009). On the other hand, when HAB in the ARP or RIS group were compared with our healthy control subjects with the use of ANCOVA (using age and sex as covariates), ARP or RIS group data were significantly different than that of control subjects (Supplementary Table 1; P_{ARP}= 0.00000109 and P_{RIS}=0.00840). Also, we performed ANCOVA for comparing the PPI measures among three groups (ARP, RIS, and healthy control groups), using above two parameters (age and sex) as covariates to adjust possible confounding. We found that HAB were significantly different among the ARP, RIS, and healthy control groups with the use of ANCOVA (P=0.00000736). However, we did not detect that other PPI measures were significantly different among the ARP, RIS, and healthy control groups with the use of ANCOVA (P_{ASR}=0.514, P_{PPI82}=0.327, P_{PPI86}=0.705, and P_{PPI90}=0.288). HAB was not statistically different between the antipsychotic groups among Japanese patients with schizophrenia (Table 2). This lack of difference in HAB among the Japanese patients with schizophrenia using different antipsychotics suggested that HAB was a common endophenotype of schizophrenia. Although ASR, PPI82, and PPI86 were not different in each of the antipsychotic groups, there was no statistical difference between the ARP or RIS groups and controls when ASR, PPI82, PPI86, and PPI90 in the ARP or RIS group were compared with our 107 healthy control subjects (Supplementary Table 1). Also, PPI90 was significantly different among the antipsychotic groups. Because it was possible that ARP and RIS led to the improvement of disruption of PPI90 to the level of healthy controls, we considered that ASR, PPI82, PPI86, and PPI90 might not be an endophenotype of schizophrenia.

There are a few limitations to this study. First, there is no control in this study. We did not measure the acoustic startle response when patients participating in this study did not take antipsychotics. Because each of the startle responses measured in the ARP group in a drug-naïve state might have higher scores than those of other antipsychotic groups in a drug-naïve state, our results must be interpreted careful. However, measuring the startle response of people with schizophrenia in the drug-naïve state is very difficult. Second, the positive association may be due to a small sample size. Third, because our samples were small, the statistical errors are possible in the results of these statistical association analyses. To overcome this limitation, a replication study using larger samples or samples of other populations will be required for conclusive results.

In conclusion, ARP and RIS may improve PPI90. ASR, HAB, PPI82, and PPI86 were no different among the Japanese schizophrenic patient groups with different antipsychotics. Since HAB showed no difference between the antipsychotic groups of Japanese patients with schizophrenia, we suggest that HAB may not be influenced by several clinical factors. However, since our samples are small, it will be necessary to conduct a replication study using larger samples.

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