Dynamic Regulation of Glutamatergic Postsynaptic Activity in Rat Prefrontal Cortex by Repeated Administration of Antipsychotic Drugs

Fabio Fumagalli, Angelisa Frasca, Giorgio Racagni, and Marco Andrea Riva

Center of Neuropharmacology, Department of Pharmacological Sciences University of Milan, Milan, Italy (F.F., A.F., G.R., M.A.R.); and Istituto di Ricoercere e Cura a Carattere Scientifico, San Giovanni di Dio-Fatebenefratelli, Brescia, Italy (G.P.)

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ABSTRACT

Antipsychotics are the mainstay for the treatment of schizophrenia. Although these drugs act at several neurotransmitter receptors, they are expected to elicit different neuroadaptive changes at structures relevant for schizophrenia. Because glutamatergic dysfunction plays a role in the pathophysiology of schizophrenia, we focused our analysis on glutamatergic neurotransmission after repeated treatment with antipsychotic drugs. Rats were exposed to a 2-week pharmacological treatment with the first generation antipsychotic haloperidol and the second generation antipsychotic olanzapine. By using Western blot and immunoprecipitation techniques, we investigated the expression, trafficking, and interaction of essential components of glutamatergic synapse in rat prefrontal cortex. Prolonged treatment with haloperidol, but not olanzapine, dynamically affects glutamatergic synapse by selectively reducing the synaptic level of the obligatory N-methyl-D-aspartate (NMDA) subunit NR1, the regulatory NMDA subunit NR2A, and its scaffolding protein postsynaptic density 95 as well as the trafficking of subunit 1 of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor to the membrane. In addition, haloperidol alters total as well as phosphorylated levels of calcium calmodulin kinase type II at synaptic sites and its interaction with the regulatory NMDA subunit NR2B. Our data suggest that the glutamatergic synapse is a vulnerable target for prolonged haloperidol treatment. The global attenuation of glutamatergic function in prefrontal cortex might explain, at least in part, the cognitive deterioration observed in patients treated with haloperidol.

Antipsychotics are the cornerstone for the treatment of schizophrenia. There is a general agreement indicating that first generation antipsychotics (FGAs) are efficacious against positive symptoms, whereas second generation antipsychotics (SGAs) may also ameliorate negative symptoms and cognitive deterioration (Keefe et al., 2006), although recent evidence has challenged this notion (Lieberman, 2007). Nevertheless, full therapeutic activity with FGAs and SGAs can only be achieved after long-term administration, implying that adaptive changes may be required in specific systems or circuitries involved in disease symptomatology (Meltzer, 1996).

Although the prevailing hypothesis for the pathophysiology of schizophrenia tends to correlate the disorder with a dysfunction of dopaminergic neurotransmission (Duncan et al., 1999), a glutamatergic hypothesis of schizophrenia has been put forward, suggesting that a deficit of glutamate neurotransmission might underlie specific aspects of this mental disorder (Jentsch and Roth, 1999; Pilowsky et al., 2006). This hypothesis stems from the evidence that pharmacological (phencyclidine) or genetic (NR1 knockdown mice) reduction of NMDA receptor function yields a remarkable similarity to psychotic states and cognitive deficits observed in schizophrenic patients (Mohn et al., 1999; Olney et al., 1999; Lindsley et al., 2006; Kristiansen et al., 2007).

The above evidence has fueled the investigation of the changes brought about by repeated antipsychotic drug treatment on the glutamatergic system. Evidence exists that available pharmacotherapy shows a differential ability in modulating glutamatergic neurotransmission, primarily via...
the modulation of ionotropic receptor expression (Fitzgerald et al., 1995; Healy and Meador-Woodruff, 1997; Riva et al., 1997; Tascetta et al., 1999; Schmitt et al., 2003; Tarazi et al., 2003; O’Connor et al., 2006). The different impact of SGAs versus FGAs is also in agreement with the observation that only the former agents are able to revert phencyclidine-induced disruption of “prepulse inhibition” (Keith et al., 1991; Bakshi and Geyer, 1995), a valuable tool to measure deficits in gating of cognitive and sensory information, which is reduced in schizophrenic patients (for review, see Braff et al., 2001).

However, it is known that glutamate function is finely tuned at synaptic level through the clustering of ionotropic receptor subunits (AMPA and NMDA) and scaffolding proteins in the postsynaptic densities, a key mechanism to activate selected intracellular signaling pathways and regulate the function at excitatory synapses. On this basis, we incorporated long-term treatments with two representative members of antipsychotic drugs (i.e., the FGA haloperidol and the SGA olanzapine) to evaluate the plasticity of the glutamatergic synapse in prefrontal cortex, a region that contributes most to the cognitive impairments observed in schizophrenic patients (Weinberger et al., 2001). Toward this goal, we focused our analysis on investigating the expression and interaction of proteins forming NMDA glutamate receptor complexes at postsynaptic density as well as AMPA subunit expression and trafficking in rat prefrontal cortex.

Materials and Methods

Materials. General reagents were purchased from Sigma-Aldrich (St. Louis, MO). Molecular biology reagents were obtained from CELBIO EuroClone (Milan, Italy) and Sigma-Aldrich. Olanzapine was a generous gift from Eli Lilly (Sesto Fiorentino, Italy), whereas haloperidol was purchased from Sigma-Aldrich.

Animal Treatments. Male Sprague-Dawley rats (Charles River Italia, Calco, Italy) weighing 225 to 250 g were used throughout the experiments. Animals were allowed to adapt to laboratory conditions for 2 weeks before any treatment and handled 5 min a day during this period; in addition, they were maintained under a 12/12-h light/dark cycle with food and water available ad libitum. Animals received daily injections of either vehicle (saline), the FGA haloperidol (1 mg/kg), or the SGA olanzapine (2 mg/kg, twice daily) for 14 days and were sacrificed 24 h after the last drug injection. Vehicle, haloperidol, or olanzapine were administered s.c. The length of the treatment and the time of sacrifice were consistent with our previous experiments showing adaptive changes with psychotroic drugs (Fumagalli et al., 2006). The doses of haloperidol and olanzapine were chosen in accordance with their receptor occupancy (Bymaster et al., 1996; Richelson, 1996; Schotte et al., 1996) and to achieve plasma levels within a therapeutic range for the treatment of schizophrenia (Andersson et al., 2002). All animal handling and experimental procedures were performed in accordance with the EC guidelines (EEC Council Directive 86/609 1987) and with the Italian legislation on animal experimentation (Decreto Legislativo 116/92).

Preparation of Protein Extracts. Brain regions were immediately dissected, frozen on dry ice, and stored at −80°C. The prefrontal cortex (defined as Cg1, PL, and IL subregions corresponding to the plates 6–10) was dissected from 2-mm-thick slices, according to the atlas of Paxinos and Watson (1996), whereas hippocampus (including both ventral and dorsal parts) was dissected from the whole brain. Different subcellular fractions were prepared as described previously (Gardoni et al., 2003). Tissues were homogenized in a Teflon-glass potter in ice-cold 0.32 M sucrose containing 1 mM HEPES, 1 mM MgCl₂, 1 mM EDTA, 1 mM NaH₂PO₄, and 0.1 mM phenylmethylsulfonyl fluoride, pH 7.4, in the presence of a complete set of protease and phosphatase inhibitors. The homogenized tissue was centrifuged at 100,000 g for 10 min to separate a pellet (P1) enriched in nuclear components from the supernatant (S1). The resulting supernatant (S1) was centrifuged at 13,000 g for 15 min to obtain a clarified fraction of cytosolic proteins (S2). The pellet (P2), corresponding to a crude membrane fraction, was resuspended in 1 mM HEPES plus protease and phosphatase inhibitors and centrifuged at 100,000 g for 1 h. The resulting supernatant (S4), referred to as Triton X-100-soluble fraction (TSF), was stored at −20°C; the pellet (P4), referred to as the Triton X-100-insoluble fraction (TIF), was homogenized in a glass-glass potter in 20 mM HEPES and protease and phosphatase inhibitors and stored at −20°C in the presence of glycerol 30%. Total protein content was measured in the subcellular fractions with the use of a protein assay (Bio-Rad Laboratories, Hercules, CA).

Western Blot Analysis. Western blot analyses were performed in homogenate, TIF, and S2 fraction. Equal amount of proteins (10 μg for S2 and homogenate; 5 μg for TIF) were electrophoretically run on an SDS-8% polyacrylamide gel under reducing conditions. Nitrocellulose membranes (Bio-Rad Laboratories) were blocked with 10% nonfat dry milk in TBS/0.1% Tween 20 buffer and then incubated with primary antibody. The conditions of the primary antibodies were as follows: phospho-NR2B (Ser1303) (1:1000 in 5% albumin; Millipore, Billerica, MA), NR2B (1:1000 in 3% nonfat dry milk; Zymed Laboratories, South San Francisco, CA), NR2A (1:1000 in 3% nonfat dry milk; Zymed Laboratories), NR1 (1:1000 in 3% nonfat dry milk; Zymed Laboratories), postsynaptic density 95 (PSD95) (1:4000 in 3% nonfat dry milk; Affinity Bioreagents, Golden, CO), synapse-associated protein 102 (SAP102) (1:1000 in 5% nonfat dry milk; Affinity Bioreagents), p-CaMKII (Thr286) (1:2500 in 3% nonfat dry milk; Affinity Bioreagents), CaMKII (1:10,000 in 3% nonfat dry milk; Millipore Bioscience Research Reagents, Temecula, CA), p-GluRII/Ser831 (1:1000 in 5% albumin; Millipore Bioscience Research Reagents), GluR1 (1:2000 in 5% albumin; Millipore Bioscience Research Reagents), GluR2 (1:2000 in 5% albumin; Millipore Bioscience Research Reagents), and β-actin (1:10,000 in 3% nonfat dry milk; Sigma-Aldrich). After 3 to 10 min washes in TBS/Tween 20, the blots were incubated 1 h at room temperature with horseradish peroxidase-conjugated secondary antibody (anti-rabbit or anti-mouse IgG; Sigma), and immunocomplexes were visualized by chemiluminescence using the ECL Western blotting kit (GE Health care, Chalfont St. Giles, Buckinghamshire, UK) according to the manufacturer’s instructions.

The blots were first probed with antibodies against the phosphorylated forms of the protein and then stripped with 2% SDS, 100 mM β-mercaptoethanol, and 62.5 mM Tris-HCl, pH 6.7, at 50°C for 30 min and then reprobed with antibodies against total proteins of the same type. Results were standardized to a β-actin control protein, which was detected by evaluating the band density at 43 kDa.

Immunoprecipitation Experiments. Aliquots of 100 μg of crude membrane fraction (P2) were incubated with antibodies against NR2B (dilution, 1:25; Zymed Laboratories) overnight at 4°C, in 1× radiolabelling buffer (200 mM NaCl, 10 mM EDTA, 10 mM NaH₂PO₄, 0.5% Nonidet P-40, pH 7.4, in the presence of a complete set of protease inhibitors) and 1% SDS. Protein A beads (Sigma) were added to each sample and incubated at 4°C for 3 h. Samples were centrifuged, and protein A beads were collected and washed three times in 1× radiolabelling buffer (1× radiolabelling buffer plus 0.1% SDS). Sample buffer (3×; 50 μl for each sample) was added, and the final mixture was boiled for 5 min. Protein A beads were pelleted by centrifugation at 14,000 g, and supernatants were loaded on a SDS-7% polyacrylamide gel under reducing conditions. Nitrocellulose membranes (Bio-Rad Laboratories) were blocked with 10% nonfat dry milk in TBS/0.1% Tween 20 buffer and then incubated with primary antibody for p-CaMKII (Thr286) (Promega, Madison, WI; dilution, 1:500 in 3% nonfat dry milk) and aCaMKII (Santa Cruz Biochemicals, Santa Cruz, CA; dilu-
tion, 1:1000 in 3% nonfat dry milk). After rinsing the membranes in TBS/Tween 20, anti-rabbit horseradish peroxidase-conjugated secondary antibody was added at 1:500 dilution, and immunocomplexes were visualized by chemiluminescence using the ECL Western Blotting kit (GE Healthcare) according to the manufacturer's instructions. Data were normalized for NR2B (Zymed Laboratories; dilution, 1:250 in 3% nonfat dry milk).

**Statistical Analysis.** Expression and phosphorylation states of the proteins of interest were measured using Quantity One software from Bio-Rad Laboratories. The mean value of the control group within a single experiment was set at 100, and the data of animals injected with olanzapine or haloperidol were expressed as “percentages” of saline-treated animals. Statistical evaluation of the changes in the phosphorylation state or expression of proteins produced by antipsychotics in prefrontal cortex was performed using a one-way analysis of variance (ANOVA) followed by Fisher's PLSD. Significance for all tests was assumed at $p < 0.05$.

**Results**

We performed an analysis of key components of glutamatergic postsynaptic transmission after prolonged antipsychotic treatment by investigating the expression of proteins and their phosphorylation state in a subcellular fraction enriched in postsynaptic densities (TIF). The effectiveness of the preparation was confirmed by the use of protein markers for specific subcellular compartments (Fig. 1). As reported by Gardoni et al. (2003), the scaffolding protein PSD95 and NMDA receptor subunits NR2A and NR2B were found enriched in crude synaptosomal fraction (P2) and TIF, with a lower abundance in total homogenate (H), whereas they were not detectable in the cytosolic compartment (S2) or in the TSF. As expected, the expression of synaptophysin, a synaptic vesicle membrane protein expressed in the presynaptic compartments, was concentrated in P2 and TSF, whereas it was weakly detected in the S2 fraction and TIF. Finally, αCaMKII was distributed throughout the fractions, although strongly enriched in TIF as previously reported (Gardoni et al., 2003).

We first examined whether antipsychotic drug treatment might affect the levels of synaptic NMDA receptors in rat prefrontal cortex. We found that repeated administration of haloperidol significantly reduced NR1 (−19%) and NR2A (−25%) expression in the TIF, without altering the levels of NR2B (Fig. 2A). Under the same experimental conditions, olanzapine did not produce any change in the synaptic levels of NMDA receptor subunits (Fig. 2A). To evaluate the regional specificity of the effects on synaptic NMDA receptors, we analyzed the expression of NMDA receptor subunits in the hippocampus. Figure 2B shows that both haloperidol and olanzapine did not alter NMDA receptor subunit levels in the TIF of this brain region. Because haloperidol shows a regional specific effect on cortical NMDA receptors, we focused our attention on molecular mechanisms underlying NMDA activation in the prefrontal cortex.

Because synaptic expression of NMDA subunits is strictly dependent upon binding with scaffolding proteins (Steigerwald et al., 2000; Scott et al., 2001), we next analyzed two membrane-associated guanylate kinases, SAP102 and PSD95. Western blot analysis revealed that haloperidol, but not olanzapine, caused a significant decrease of PSD95 (−22%), with no effect on SAP102 (Fig. 3).

Changes in synaptic NMDA composition after haloperidol treatment might alter receptor kinetics and calcium permeability (Monyer et al., 1994). Because αCaMKII represents the major target of calcium influx through synaptic NMDA receptors, we reasoned that the changes produced by haloperidol on NMDA receptors could influence the expression of synaptic levels of NMDA receptor subunits in prefrontal cortex and hippocampus after prolonged antipsychotic drug treatment.
and activation state of this kinase. As shown in Fig. 4A, prolonged administration of haloperidol significantly reduced total (−25%) as well as p-αCaMKII(Thr286) (−21%) levels in the TIF. This effect was confined to the synaptic compartment because no significant changes were observed in the crude homogenate (Fig. 4B). Conversely, olanzapine did not modify αCaMKII expression and phosphorylation in any cellular compartment (Fig. 4).

After autophosphorylation, αCaMKII is known to interact with the NR2B subunit, thus ensuring a Ca²⁺/calmodulin-independent kinase activity (Bayer et al., 2001). To establish possible changes in αCaMKII-NR2B interaction, we immunoprecipitated NR2B (whose expression is not altered by the pharmacological treatment, see Fig. 2), and measured both p-αCaMKII(Thr286), as well as αCaMKII levels. Our results indicate that haloperidol, but not olanzapine, reduced such interactions (−33% for p-αCaMKII(Thr286) and −42% for αCaMKII) (Fig. 5). p-αCaMKII(Thr286), after interacting with NR2B, phosphorylates this NMDA subunit in Ser1303 (Okumura et al., 1996); however, Western blot experiments revealed that such phosphorylation was not modified by either olanzapine or haloperidol (Fig. 6).

Several lines of evidence have demonstrated that, within the PSD, αCaMKII is also involved in the modulation of AMPA receptors. In particular, αCaMKII governs GluR1 trafficking to synaptic sites (Hayashi et al., 2000). Hence, to investigate the possible consequences of reduced synaptic

![Fig. 3. Modulation of synaptic levels of NMDA receptor scaffolding proteins in prefrontal cortex after prolonged antipsychotic drug treatment. Top, a representative immunoblot of PSD95 and SAP102 in the TIF of rat prefrontal cortex after repeated treatment with haloperidol (H) and olanzapine (O), compared with vehicle-injected animals (S). Rats (n = 6 for each group) were killed 24 h after the last drug injection. Bottom, the quantitative data (mean ± S.E.M), expressed as percentage of control rats. *, p < 0.05 versus controls (one-way ANOVA followed by Fisher's PLSD).](image)

![Fig. 4. Modulation of p-αCaMKII(Thr286) and total αCaMKII levels in rat prefrontal cortex after prolonged antipsychotic drug treatment. Representative immunoblots of p-αCaMKII(Thr286) and αCaMKII in the TIF (A) and homogenate (B) are shown at the top after repeated treatment with haloperidol (H) and olanzapine (O), compared with vehicle-injected animals (S). Rats (n = 6 for each group) were killed 24 h after the last drug injection. Bottom, the quantitative data (mean ± S.E.M), expressed as percentage of control rats, in TIF and homogenate (n = 6 for each group). *, p < 0.05; **, p < 0.01 versus controls (one-way ANOVA followed by Fisher's PLSD).](image)

![Fig. 5. Modulation of p-αCaMKII(Thr286)-NR2B interaction in rat prefrontal cortex after prolonged antipsychotic drug treatment. Top, a representative immunoblot of p-αCaMKII(Thr286) immunoprecipitated with NR2B in the three experimental groups. Bottom, the quantitative analysis of p-αCaMKII(Thr286) associated with the regulatory subunit NR2B (n = 6 for each group). ***, p < 0.01 versus controls (one-way ANOVA followed by Fisher's PLSD).](image)
αCaMKII levels on AMPA receptor trafficking, we examined two AMPA receptor subunits, namely GluR1 and GluR2, in different cellular fractions from the prefrontal cortex of rats undergoing long-term treatment with haloperidol or olanzapine. We found that synaptic levels (TIF) of GluR1 expression were significantly reduced by repeated haloperidol treatment (−20%), but not olanzapine (Fig. 7A). To establish whether this effect was due to a deficit of protein synthesis rather than trafficking mechanisms, we analyzed GluR1 levels in the homogenate and cytosolic fraction of prefrontal cortex. No changes were observed in crude homogenate after treatment with both antipsychotics, whereas haloperidol significantly increased the levels of GluR1 in the cytosolic compartment (+74%) (Fig. 7A) but not of GluR2 in all cellular fractions investigated (Fig. 7B). Besides altering protein trafficking, long-term haloperidol treatment reduced GluR1 phosphorylation on the Ser 831 residue by αCaMKII (−26%) (Fig. 8).

Discussion

We report here notable disparities between haloperidol and olanzapine in the modulation of ionotropic glutamate receptors in the postsynaptic compartment of rat prefrontal cortex. Although the SGA olanzapine preserves glutamatergic function at PSD, we found that repeated administration of haloperidol markedly affects postsynaptic density organization and function.

Although previous studies on the topic have looked at the effects of antipsychotic treatment on mRNA levels or total protein expression (Fitzgerald et al., 1995; Healy and Meador-Woodruff, 1997; Riva et al., 1997; Tasedda et al., 1999; Schmitt et al., 2003; Tarazi et al., 2003; O'Connor et al., 2006), our study examines how antipsychotics may regulate these “glutamatergic” proteins at synaptic level, how they are dynamically trafficked in the cell, and how they differentially interact with each other to regulate phosphorylation states and, ultimately, the functional activity of glutamatergic receptors. We here report for the first time that antipsychotics can modulate the glutamatergic system, namely the expression of receptor subunits, scaffolding, and signaling proteins, in an enriched postsynaptic fraction (TIF) of prefrontal cortex, which has direct implications for glutamatergic function and responsiveness. We found that haloperidol reduced the synaptic levels of the NMDA obligatory subunit NR1 and the regulatory subunit NR2A, but not NR2B, which might lead to altered kinetic properties of the ionotropic receptor (Monyer et al., 1994; Nabekura et al., 2002). The decrease of synaptic NMDA receptor expression after haloperidol treatment is supported by the evidence that the expression of the scaffolding protein PSD95 is also reduced. To this end, a lower expression of NMDA receptor subunits and scaffolding proteins is also observed in prefrontal cortex of schizophrenics (Ohnuma et al., 2000; Toyooka et al., 2002; Kristiansen et al., 2006). Note that the diminished availability of active NMDA receptor is not observed in hippocampus, thus highlighting the regional selectivity of the changes brought about by haloperidol. The evidence that the expression of NR1, NR2A,
and PSD95 is not altered in the crude homogenates (data not shown) allows us to suggest that haloperidol affects the synaptic expression of these proteins, probably through an alteration of their trafficking to the synaptic compartment.

NMDA receptor activation drives calcium entry into the cell that, on its turn, activates different intracellular pathways. Hence, it is feasible to hypothesize that haloperidol might attenuate postsynaptic responses associated with calcium influx. A primary target of postsynaptic calcium elevation through NMDA receptor is αCaMKII, which immediately undergoes autophosphorylation in Thr286 and interacts with the regulatory subunit NR2B, locking itself in an activated state, thus prolonging its synaptic activity (Bayer et al., 2001). We found that haloperidol reduced total as well as p-αCaMKII(Thr286) levels in the synaptic compartment, but not in the crude homogenate, of prefrontal cortex, suggesting that kinase recruitment at postsynaptic sites is compromised, presumably because of an altered trafficking rather than to a reduction of αCaMKII synthesis. Accordingly, the reduction of αCaMKII, in its total and phosphorylated form, after long-term haloperidol treatment leads to a significant decrease of its interaction with NR2B, as indicated by immunoprecipitation experiments, which might impair NMDA function at the synaptic level. The observation that NR2B phosphorylation at Ser 1303 by αCaMKII (Omkumar et al., 1996) was not altered after haloperidol administration suggests that treatment with the FGA alters the trafficking of the kinase to the postsynaptic compartments rather than its activity on the NMDA complex.

Conversely, reduced synaptic levels of αCaMKII in haloperidol-treated rats were paralleled by a significant decrease of GluR1 levels in the same fraction and a concomitant increase in the cytosol. Because GluR1 trafficking is dependent on synaptic activity and αCaMKII (Hayashi et al., 2000; Gao et al., 2006), reduced levels of this kinase at excitatory synapse might impair the trafficking of this AMPA receptor subunit from the cytosol to the synaptic compartment. To this end, the specificity of this effect is suggested by the observation that GluR2 incorporation into synapse is not altered by the treatment, possibly because this receptor subunit may be constitutively delivered to the membrane, independently from neuronal activity (Passafaro et al., 2001).

Taken as a whole, it is reasonable to assume that the changes produced by repeated treatment with haloperidol converge to determine a global dysfunction of glutamatergic synapse in rat prefrontal cortex. The decreased availability of NR1, NR2A, PSD95, and αCaMKII at postsynaptic density as well as reduced delivery of GluR1 into the synapse might represent a deleterious mechanism altering synaptic plasticity within prefrontal cortex (Migaud et al., 1998; Haucke, 2000). However, the observation that dysregulation of PSD95 may lead to altered plasticity after long-term exposure to cocaine (Yao et al., 2004) points to this scaffolding protein as a common mediator of addictive and psychiatric disorders and provides additional mechanistic evidence for monoaminergic modulation of glutamatergic neurotransmission that could play a role in the herein reported effects of haloperidol.

The temporal sequence of these events remains elusive; however, we favor the possibility that, as a first step, pro-
longed treatment with haloperidol reduces synaptic NMDA subunit expression and alters its composition, thus limiting NMDA-mediated transmission. Such an effect might compromise calcium influx that, in turn, leads to a diminished recruitment of αCaMKII to synaptic sites. Reduced availability of synaptic αCaMKII might be responsible for alterations in GluR1 trafficking to postsynaptic density, leading to an impaired function of AMPA receptors (Fig. 9). Although this study has been conducted in “normal animals,” our data suggest the possibility that haloperidol might “worsen” the function of the glutamatergic system, which can already be defective in schizophrenia (Jentsch et al., 1999). In summary, our data provide evidence that haloperidol induces an orchestrated deficiency of glutamatergic postsynaptic functions. Although we are aware that the prefrontal cortex is only one part of a much larger and complicated circuit that governs cognitive functions, given the prominent role of glutamate in cognition, it is conceivable to hypothesize that such changes may contribute to learning and memory deterioration observed in humans after exposure to the drug (Zirnheld et al., 2004; Castner and Williams, 2007; Mouri et al., 2007).

References