

Regulation of Ionotropic Glutamate Receptors in the Rat Brain in Response to the Atypical Antipsychotic Seroquel (Quetiapine Fumarate)

F. Tascedda, Ph.D., E. Lovati, M.A., J.M.C. Blom, Ph.D., P. Muzzioli, M.A., N. Brunello, Ph.D., G. Racagni, Ph.D., and M.A. Riva, Ph.D.

The interplay between dopamine and glutamate appears to be relevant in the etiopathology of schizophrenia. Although currently used antipsychotics do not interact with glutamatergic receptors, previous results have demonstrated that the expression profile of ionotropic glutamate receptors can be regulated by drugs such as haloperidol or clozapine. In the present investigation, the mRNA levels for NMDA and AMPA receptor subunits were measured after chronic treatment with the novel antipsychotic agent Seroquel (quetiapine fumarate, quetiapine) as compared to haloperidol and clozapine. Similarly to the prototype atypical clozapine, quetiapine

reduced the mRNA expression for NR-1 and NR-2C, two NMDA forming subunits, in the nucleus accumbens. Furthermore, quetiapine, but not haloperidol or clozapine, increased the hippocampal expression for the AMPA subunits GluR-B and GluR-C. The differences between classical and atypical antipsychotics, as well as among the novel agents, might be relevant for specific aspects of their therapeutic activity and could provide valuable information for the role of glutamate in specific symptoms of schizophrenia. [Neuropsychopharmacology 21:211–217, 1999] © 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

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In light of the knowledge accumulated during the past couple of decades, it is apparent that schizophrenia is a complex and heterogeneous disease (Lieberman and Koren 1993). Even though, classical neuroleptics are clearly useful in the treatment of positive aspect of the disease, they have a limited efficacy on negative symptoms and cognitive deterioration (Meltzer 1991). Conversely, clozapine and the novel antipsychotics have been termed 'atypicals' because they have a lower inci-

dence of extrapyramidal side effects and can be effective in the treatment of negative symptoms (Deutch et al. 1991; Kinon and Lieberman 1996).

The molecular basis of these differences has not been clearly established, but could be related to receptor profiles, regional specificity within the CNS and the possibility to produce adaptive changes in specific neurotransmitter systems whose function is altered in schizophrenia (Ellenbroek 1993). Among the others, dopamine, glutamate, and their reciprocal interactions within discrete neuronal circuitry, can be viewed as major players in schizophrenia imbalance (Weinberger 1987; Carlsson and Carlsson 1990; DiChiara et al. 1994). Hyperdopaminergic activity is thought to be relevant for positive symptoms of the disease, whereas alterations in glutamatergic system could explain several features of the disorder including negative symptoms and cognitive dysfunctions (Olney and Farber 1995; Weinberger and Lipska 1995). Hence, on the basis of its functional interaction with dopamine, glutamate and

From the Center for Neuropharmacology, Institute of Pharmacological Sciences (FT, NB, GR, MAR, EL), University of Milan, Milan, Italy; Department of Pharmaceutical Sciences (FT, JMCB, PM, NB), University of Modena, Modena, Italy; and I.R.C.C.S. (GR, JMCB), San Giovanni di Dio-Fatebenefratelli, Brescia, Italy.

Address correspondence to: M.A. Riva, Center for Neuropharmacology, Via Balzaretti 9, 20133 Milan, Italy.

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its receptors might be modulated in response to drugs that interfere with the dopaminergic system. Furthermore, the blockade of different neurotransmitter receptors, as occurring with novel antipsychotics, might have a different impact on glutamatergic system as compared to classical neuroleptics.

Recently, a number of different laboratories, including our own, have examined the regulation of glutamate receptors in response to treatment with haloperidol and clozapine (Fitzgerald et al. 1995; Riva et al. 1997; Healy and Meador-Woodruff 1997; Brené et al. 1998). In the present study, we investigated the modulation of the mRNA encoding for NMDA and AMPA glutamate receptor subunits in response to the atypical antipsychotic drug "Seroquel (quetiapine fumarate, quetiapine)" (Goldstein 1996).

In order to gain insight in the possible relationships between the changes in glutamate receptor expression and the clinical properties of the drug, we have compared the effects elicited by quetiapine to those observed with haloperidol and clozapine, the prototypes for classical and atypical antipsychotics.

MATERIALS AND METHOD

Male Sprague Dawley rats (Charles River, Calco, Italy) weighing 250–350 g were used throughout the experiments. The animals were maintained under a 12 hr light/12 hr dark cycle with food and water available *ad libitum*. Animals received daily subcutaneous injections with saline, haloperidol (1 mg/kg), clozapine (30 mg/kg), or quetiapine (25 mg/kg) for 21 days. Rats were sacrificed by decapitation 6 hr after the last injection. The brain regions were rapidly dissected, frozen in liquid nitrogen, and stored at -70°C for further analysis. All animal manipulations have been carried out in accordance with the Guide for the Care and Use of Laboratory Animals.

RNA Isolation

Different brain regions were homogenized in 4 M guanidinium isothiocyanate (containing 25 mM sodium citrate pH 7.5, 0.5% sarcosyl, and 0.1% 2-mercaptoethanol) and total RNA was isolated by phenol-chloroform extraction (Chomczynski and Sacchi 1987). Quantification was carried out by absorption at 260 nm and RNA was re-precipitated in ethanol for RNase protection assay.

Probe Preparation and RNase Protection Assay

The cDNAs for the different NMDA or AMPA receptor subunits were arranged in order to obtain proper templates for the *in vitro* transcription of cRNA probes to be used in the RNase protection assay (Riva et al. 1997).

The cRNA probes for NMDA and AMPA receptor subunits and the relative protected fragment (p.f.) were the following: NR-1 = 438, p.f. = 414; NR-2A = 187, p.f. = 171; NR-2B = 310, p.f. = 264; NR-2C = 244, p.f. = 213; GluR-A = 447, p.f. = 400; GluR-B (flip-flop) = 360, p.f.(flip) = 300, p.f.(flop) = 170; GluR-C = 602, p.f. = 570; GluR-D = 760, p.f. = 700. pTRI-actine-Rat (Ambion) containing a portion of rat β -actine cDNA of 195 with a p.f. = 126.

The RNase protection assay was performed on a 10 μg sample of total RNA as described previously (Riva et al. 1997). Briefly, after ethanol-precipitation total RNA, obtained from different tissues, was dissolved in 20 μl of hybridization solution (80% formamide; 40 mM PIPES, pH 6.4; 400 mM sodium acetate, pH 6.4; and 1 mM EDTA) containing 150,000 cpm of each ^{32}P -labeled cRNA probes (specific activity $> 10^8$ cpm/ μg). After being heated at 85°C for 10 min, the cRNA probes were allowed to hybridise the endogenous RNAs at 45°C overnight. At the end of the hybridization, the solution was diluted with 200 μl of RNase digestion buffer (300 mM NaCl; 10 mM Tris HCl, pH 7.4; and 5 mM EDTA, pH 7.4) containing a 1/200 dilution of a RNase cocktail (1 mg/ml RNase A and 20 U/ml RNase T1) and incubated for 30 min at 30°C . Proteinase K (10 μg) and SDS (10 μl of 20% stock solution) were then added to the sample and the mixture was incubated at 37°C for an additional 15 min. At the end of the incubation the sample was extracted with phenol/chloroform and ethanol precipitated.

The pellet (containing the RNA:RNA hybrids) was dried and resuspended in loading buffer (80% formamide, 0.1% xylene cyanol, 0.1% bromophenol blue, and 2 mM EDTA), boiled at 95°C for 5 min and separated on a 5% polyacrylamide gel under denaturing conditions (7 M urea). The protected fragments were visualized by autoradiography.

Western Blot Analysis of GluR-B Subunit

Hippocampus from control and drug-injected animals were homogenized on ice cold RIPA Buffer (1x PBS, 1% Igepal CA630, 0.5% sodium deoxycholate, 0.1% SDS, 10 mg/ml PMSF, Aprotinin 30 $\mu\text{l}/\text{ml}$, and 100mM sodium orthovanadate). Samples were clarified by centrifugation at 15000g for 20 min at 4°C . Following protein determination (BCA protein assay reagent kit, Pierce), samples (20–40 $\mu\text{g}/\text{lane}$) were run on SDS-7.5% polyacrylamide gel under reducing conditions. Proteins were transferred electrophoretically to nitrocellulose membrane (Biorad, Milan, Italy). The GluR-B subunit (MW 108 kDa) was immunolabeled using a rabbit polyclonal antibody (Chemicon, Temecula, CA, USA) diluted 1:200, followed by anti rabbit IgG peroxidase conjugate (Santa Cruz, Santa Cruz, CA). Immuno-complexes were visualized by chemiluminescence utilizing the Western

Blot Chemiluminescence Reagent Plus kit (Dupont NEN, Cologno Monzese, Italy). Optical densities from different Western experiment were first converted to percent of control values and then analyzed by χ^2 tests.

RNA Calculation and Statistical Analysis

The levels of mRNA for NMDA and AMPA receptor subunits were obtained by densitometry measurements of autoradiographies analyzed with a LKB laser densitometer. Optical densities from all experimental groups were analyzed by ANOVA. Individual group differences were further analyzed by Dunnett-*t*-test. Optical densities from experimental groups treated chronically with antipsychotic drugs were then expressed and presented as mean percent of control values for graphic clarity, that is, NMDA or AMPA receptor subunit/ β -actin levels were expressed as percentage of saline-injected animals. β -actin was employed as internal standard for RNase protection assay and did not differ across experimental groups. Statistical differences were considered significant when $p > .05$ (ANOVA and Dunnett-*t*-test).

RESULTS

NMDA and AMPA are two glutamate receptor subtypes expressed in several rat brain structures. Each of these receptors is composed by different subunits which confer specific electrophysiological, pharmacological, and functional properties to the channel (Seeburg 1993; Hollmann and Heinemann 1994). Changes in the expression profile of these subunits in response to different stimuli might alter the response of specific cells to glutamate.

Figure 1 summarizes the effects of a chronic treatment with quetiapine on the mRNA levels for NMDA receptor subunits in rat hippocampus, striatum, and nucleus accumbens. The injection of the drug did not produce any change in the hippocampus. Similarly the expression of NR-1, NR-2A, and NR-2B in the striatum was not altered and only a small, although significant, increase in the levels for NR-2C mRNA in this structure was detected. Conversely, chronic administration of quetiapine produced a significant reduction of NR-1 and NR-2C mRNA levels in the nucleus accumbens, an effect we had previously observed with clozapine but not classical neuroleptics (Riva et al. 1997).

Subsequently, we investigated, under the same experimental conditions, the expression profile for AMPA receptor subunits. We found that quetiapine, as well as haloperidol and clozapine, did not affect GluR-A, -B and -C mRNA levels in the striatum. Haloperidol was also ineffective in modulating AMPA receptor subunits in hippocampus and nucleus accumbens (Table 1 and

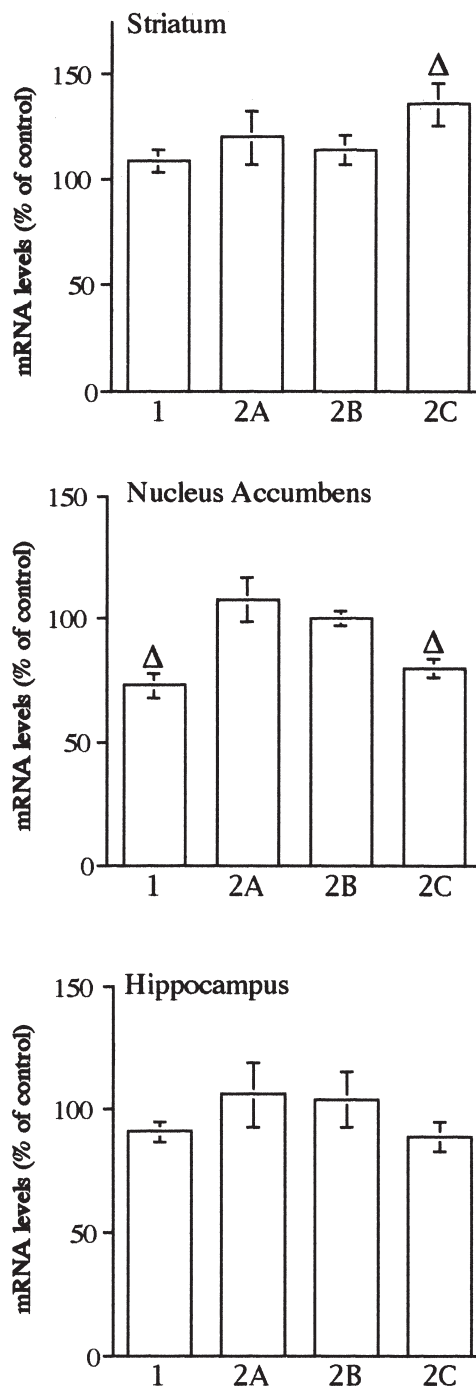


Figure 1. Effect of chronic administration of quetiapine (25 mg/kg, s.c. daily for 21 days) on NMDA-R subunit mRNA levels in rat striatum, nucleus accumbens, and hippocampus. Rats were killed 6 hr after the last injection and mRNA determination was carried out by RNase protection assay, as described in Materials and Methods. The results, expressed as percentage of saline-injected rats, represent the mean \pm S.E.M. of at least eight independent determinations. $\Delta p < .05$ vs. saline injected rats (ANOVA with Dunnett *t*-test).

Table 1. Effect of Chronic Antipsychotic Drug Treatment on AMPA Receptor Subunit mRNA Levels in the Rat Striatum. The Results, Expressed as Percentage of Saline-Injected Animals, Represent the Mean \pm S.E.M. of 5–10 Independent Determinations

Group	GluR-A	GluR-Bi	GluR-Bo	GluR-C
	(% of control levels)			
Saline	100 \pm 8	100 \pm 13	100 \pm 11	100 \pm 16
Haloperidol	111 \pm 5	113 \pm 9	118 \pm 10	120 \pm 13
Clozapine	93 \pm 8	106 \pm 13	115 \pm 15	109 \pm 19
Quetiapine	111 \pm 9	117 \pm 15	122 \pm 14	119 \pm 14

2), whereas clozapine reduced the levels for GluR-B_{flip} and GluR-C in the nucleus accumbens without affecting their expression in the hippocampus. Interestingly, quetiapine did not change AMPA subunit expression in the nucleus accumbens but, as shown in Figure 2, increased the levels for GluR-B and GluR-C in the hippocampus. The mRNA levels for both GluR-B configurations, namely flip and flop (Seeburg 1993), were increased at the same extent without any significant change in the ratio between the two isoforms (data not shown).

In order to establish if these changes in mRNA levels do translate in protein changes, we investigated by Western blot analysis the levels for GluR-B subunit immunoreactivity. Figure 3 shows that, in agreement with the results obtained at mRNA levels, quetiapine did elevate the protein level for this receptor subunit in the hippocampus (+59%). On the contrary clozapine and haloperidol did not produce any change in the protein level for GluR-B subunit (data not shown).

DISCUSSION

The present data indicate that prolonged exposure to the novel antipsychotic quetiapine is able to modulate the expression of ionotropic glutamate receptors in selected brain structures. The anatomical pattern of these changes suggests that this atypical antipsychotic might influence the glutamatergic system in brain structures where such neurotransmitter might contribute to specific aspects of schizophrenia.

The analysis of NMDA, as well as AMPA receptor gene expression indicates that there are substantial differences in the way antipsychotic drugs might modulate their expression profile. We and others (Fitzgerald et al. 1995; Riva et al. 1997) have previously shown that NMDA receptor subunit mRNA levels are significantly increased in rat striatum following prolonged exposure to haloperidol but not to clozapine. The present results indicate that, similarly to the prototype atypical clozapine, quetiapine did not affect NMDA receptor subunit expression in the striatum, with the exception of a slight

Table 2. Effect of Chronic Antipsychotic Drug Treatment on AMPA Receptor Subunit mRNA Levels in the Rat Nucleus Accumbens. The Results, Expressed as Percentage of Saline-Injected Animals, Represent the Mean \pm S.E.M. at Least 8 Independent Determinations

Group	GLUR-A	GLUR-Bi	GLUR-Bo	GLUR-C
	(% of control levels)			
Saline	100 \pm 9	100 \pm 11	100 \pm 9	100 \pm 9
Haloperidol	97 \pm 9	111 \pm 17	110 \pm 19	101 \pm 14
Clozapine	80 \pm 9	72 \pm 9 ^a	82 \pm 10	77 \pm 10 ^a
Quetiapine	111 \pm 6	145 \pm 16	131 \pm 13	118 \pm 7

^a $p < .05$ vs. saline-injected animals.

elevation of NR-2C mRNA. The indication that NMDA receptor antagonists can antagonize haloperidol-induced catalepsy in rats (Yoshida et al. 1994) suggests that an increased function of the NMDA-R complex could contribute to the motor side effects produced by classical, but not atypical, antipsychotics. Furthermore, an increased expression of NMDA-R subunits could also play a role in excitotoxic mechanisms that might take place after long term treatment with classical neuroleptics (Nielsen and Lyon 1978). Our data are in line with this hypothesis, as quetiapine, a compound with low EPS liability, did not produce major effects at this level.

The changes of glutamate ionotropic receptor in the striatum appear to be specific for the NMDA-R subtype since the mRNA levels for AMPA receptor subunits were not significantly altered in response to antipsychotic treatment.

The nucleus accumbens represents a potential site for antipsychotic drugs, as suggested by the fact that classical as well as atypical antipsychotic produce an induction of c-fos immunoreactivity after acute administration (Robertson et al. 1994; Fink-Jensen and Kristensen 1994). This similarity can also be observed after chronic treatment as haloperidol, clozapine, and quetiapine (Vahid-Ansari et al. 1996) significantly increase the immediate early gene product Δ FosB in the nucleus accumbens. However, the effect of quetiapine, in line with our previous results with clozapine (Riva et al. 1997), indicates that only atypical drugs reduce the mRNA levels for NR-1 and NR-2C in the nucleus accumbens. This suggests that, although prolonged activation of the neurons within the nucleus accumbens may represent a common event to antipsychotic drug therapy (Robertson et al. 1994), only atypical drugs can produce adaptive changes in the expression of NMDA receptor subunits. A reduction in the expression and function of NMDA receptors within the nucleus accumbens can indeed be relevant for the pharmacological activity of these drugs. Reijmers and coworkers (1995) have shown that prepulse inhibition, a neuronal mechanism which is impaired in schizophrenics (Braff et al.

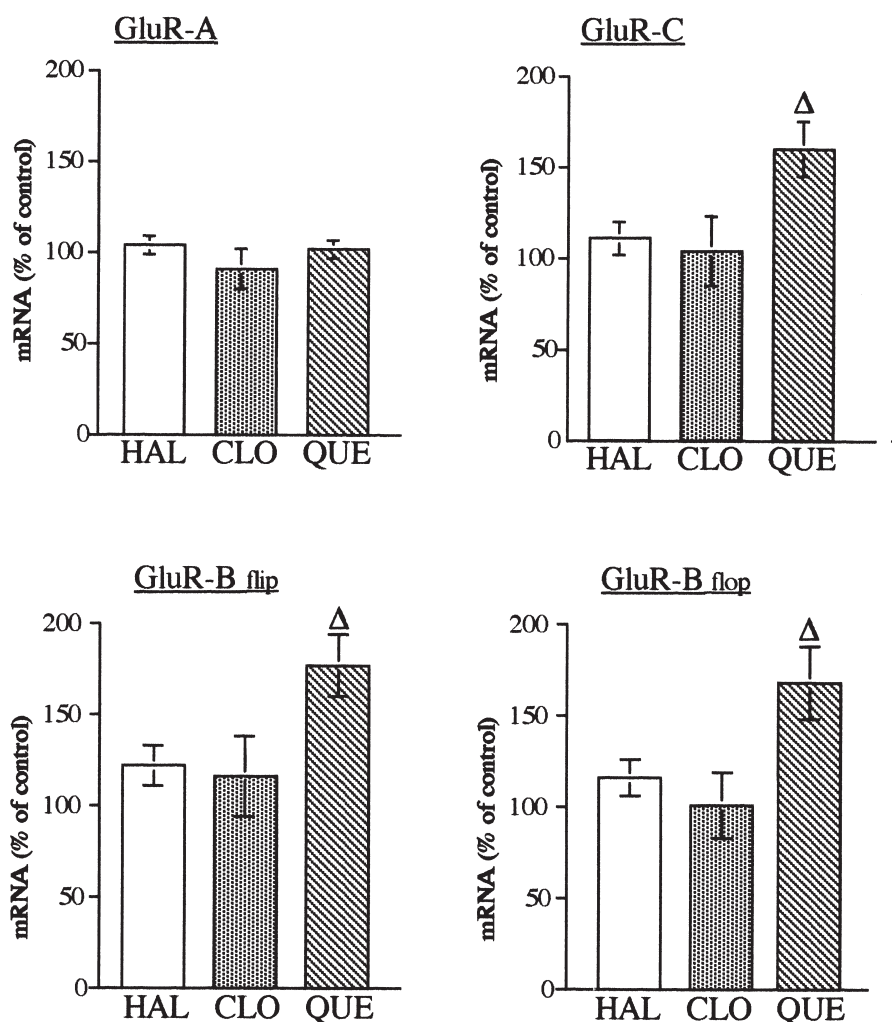


Figure 2. Determination of hippocampal mRNA levels for AMPA receptor subunits in response to chronic exposure with haloperidol (HAL), clozapine (CLO), or quetiapine (QUE). The results, expressed as percentage of vehicle injected rats, represent the mean \pm S.E.M. of 8–12 independent determinations. $\Delta p < .05$ vs. saline injected rats (ANOVA with Dunnett *t*-test).

1992; Cadenhead et al. 1993), is reduced after injection of NMDA receptor agonist within the nucleus accumbens (Reijmers et al. 1995). It is, therefore, feasible that a reduction in the expression of NMDA receptor subunits, brought about by atypical antipsychotic in this brain region, can contribute to restore normal glutamatergic neurotransmission. In line with this possibility, it has been proposed that impaired functioning of the hippocampus contributes to deficits in prepulse inhibition and this could be mediated by glutamatergic afferents to the nucleus accumbens (Caine et al. 1992). We have also observed that clozapine, but not quetiapine or haloperidol, reduces the mRNA levels for GluR-Bflip and GluR-C, two AMPA receptor subunits, suggesting that some of the adaptive mechanisms taking place in glutamatergic transmission might also involve AMPA receptors.

Neuroanatomical and chemical dysfunction of the

hippocampus are present in schizophrenia (Jeste and Lohr 1989; Benes et al. 1991; Breier et al. 1992). These alterations, through the connection of the hippocampus with other brain structures, are important to several aspects of the disease. Therefore, it was important to examine the expression for glutamate receptors as its activity within the hippocampus play a significant role in cognitive functions which are impaired in schizophrenic subjects (Donnelly et al. 1980). Although treatment with antipsychotics did not change the levels of NMDA-R subunit expression in the rat hippocampus, we found that quetiapine produced a significant elevation of the AMPA subunits, GluR-B and GluR-C. Interestingly, this effect was not mimicked by haloperidol or clozapine administration although, in a previous report, it has been shown that clozapine can elevate (+21%) GluR-B immunoreactivity in the hippocampus (Fitzgerald et al. 1995). The changes observed after

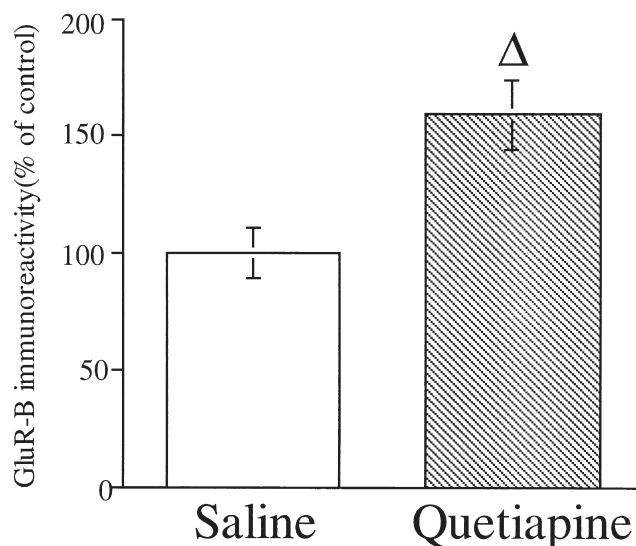


Figure 3. Level of glutamate GluR-B receptor subunit immunoreactivity in hippocampus after chronic treatment with quetiapine. The results, expressed as percentage of vehicle injected rats, were derived from two independent determinations (combined $n = 8$ /treatment group) and represent the mean \pm S.E.M. $\Delta p < .05$ vs. saline injected rats (χ^2 tests).

chronic quetiapine are interesting in relation to molecular abnormalities detected in the hippocampus of schizophrenic patients. In fact, the levels of GluR-B mRNA are significantly reduced in the hippocampal formation of schizophrenics, a modification that might contribute to specific aspect of the disease (Eastwood et al. 1997). In particular, on the basis of a glutamatergic role in cognition, a decreased expression and function of glutamatergic receptor might be relevant for the cognitive deterioration observed in schizophrenic subjects. If this is true, the effect of quetiapine, although observed in normal animals without any possible alteration in the glutamatergic system, is of great interest as it might contribute to restore normal glutamatergic function at the hippocampal level.

Quetiapine is a novel dibenzothiazepine which binds several brain receptors including dopaminergic, serotonergic, alpha adrenergic, and histaminergic. The pre-clinical profile of quetiapine shares many similarities with clozapine and these effects could be relevant for its therapeutic activity (Ellenbroek et al. 1996). For example, both drugs can increase, after chronic administration, Δ FosB immunoreactivity in the rat prefrontal cortex (Vahid-Ansari et al. 1996). As a reduced neuronal activity in this structure may be responsible for negative symptoms of schizophrenia (Andreasen et al. 1986; Weinberger and Lipska 1995), quetiapine and clozapine might improve the symptomatology by enhancing the activity of this brain structures. In line with these data and with the results we have obtained on the expression of glutamate receptors, quetiapine has been shown

to reduce positive and negative symptoms of schizophrenia without producing extrapyramidal side effects (Goldstein and Arvanitis 1995).

One of the features of novel antipsychotics is the broad profile of affinity for several neurotransmitter receptors. It will be important, therefore, to examine whether the adaptive changes observed in glutamate neurotransmission, after prolonged treatment, are due to the blockade of a specific receptor subtype or are the result of more general adaptive changes that contribute to the therapeutic activity of these molecules.

In summary, the data emerging from our study confirm that the glutamatergic system is a target for antipsychotic drug therapy with clear and relevant differences between classical and atypical drugs. However, our results also suggest that within the group of novel antipsychotics specific adaptive changes are encountered that could provide important clues on specific therapeutic action of the drugs (Arndt and Skarsfeldt 1998).

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