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# AMPA Receptor Binding and Subunit mRNA Expression in Prefrontal Cortex and Striatum of Elderly Schizophrenics

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*The dopamine hypothesis of schizophrenia has recently evolved into a model of dysfunctional integration between cortical and subcortical dopaminergic activity. Anatomical data suggest that regional alterations in dopaminergic activity may be linked by means of the rich glutamatergic innervation of the striatum by corticostriatal projections, suggesting a potential role for glutamatergic dysfunction in schizophrenia. Although pharmacological data have implicated the NMDA subtype of glutamate receptor in this illness, disturbance in AMPA receptor expression could potentially lead to the NMDA receptor hypoactivity hypothesized in schizophrenia. To address this possibility, we examined AMPA receptor binding and subunit mRNA levels in prefrontal cortex and striatum of schizophrenics and matched controls. There were no significant differences in AMPA receptor binding or subunit mRNA levels in either prefrontal cortical or striatal regions of schizophrenics. Furthermore, AMPA receptor expression did not seem to be regulated by chronic antipsychotic drug exposure, when neuroleptic treated and drug-free schizophrenics were analyzed separately. These data do not support a role for altered AMPA receptor expression in cortex and striatum in schizophrenia.*

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KEY WORDS: *Glutamate; NMDA; in situ Hybridization; Receptor autoradiography; Postmortem*

The dopamine hypothesis of schizophrenia originally postulated that excessive dopaminergic activity is associated with psychotic symptoms, but has recently evolved into a model postulating a dysfunctional integration between cortical and subcortical dopaminergic activity (Weinberger et al. 1988; Davis et al. 1991). Specifically, dopaminergic hypofunction in the cortex and hyperfunction in the striatum are hypothesized to be associated with negative and positive symptoms, respectively. The rich glutamatergic innervation of the striatum, by corticostriatal glutamatergic afferents, suggests that these regional alterations in dopaminergic activity may be linked (Carlsson and Carlsson 1990). This anatomical relationship further suggests a potential role for glutamatergic dysfunction in the pathophysiology of schizophrenia.

Glutamate is the primary excitatory neurotransmitter in the human brain. There are four families of glutamate receptors, including the ionotropic receptors, NMDA and AMPA (Hollmann and Heinemann 1994).

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These receptors are composed of combinations of subunits that assemble to form a pentameric ligand-gated ion channel (Hollmann and Heinemann). These subunits are encoded by separate genes, and each final receptor may be composed of one (homomeric) or several different subunits (heteromeric). NMDA receptor subunits are encoded by genes that have been named NMDAR1 and NMDAR2A-NMDAR2B, whereas, AMPA receptor subunits are encoded by genes named gluR1-gluR4 (Hollmann and Heinemann). These subunits confer specific functional properties to the final receptors (Hollmann et al. 1991; Burnashev et al. 1992).

NMDA receptors are most often implicated in schizophrenia, because NMDA receptor antagonists such as phencyclidine and ketamine cause psychotic symptoms in normal volunteers and exacerbate these symptoms in schizophrenics (Itil et al. 1967; Javitt and Zukin 1991; Krystal et al. 1994; Lahti et al. 1995). Furthermore, glycine (Javitt et al. 1994), which facilitates NMDA receptor-mediated neurotransmission, and the glycine site partial agonist D-cycloserine (Goff et al. 1995) have been reported to ameliorate negative psychotic symptoms. These findings have led to speculation that NMDA receptor hypofunction may be associated with some of the psychotic symptoms seen in schizophrenics. However, it is not known whether this hypoactivity may be attributable to a primary defect in NMDA receptor expression or function, or if some modulator of NMDA receptor function is deficient. One potential candidate modulator is the AMPA receptor.

AMPA receptors mediate fast glutamatergic neurotransmission, and are present in many brain regions, including the striatum and cortex (Hollmann and Heinemann 1994). AMPA receptors may also facilitate NMDA receptor activity. At rest, the ion channel of the NMDA receptor is blocked by magnesium, and partial depolarization of the cell membrane is required to extrude magnesium ions (Hollmann and Heinemann 1994). Because this voltage-dependent blockade can be overcome by AMPA receptor activation, AMPA receptor dysfunction can likely affect NMDA receptor activity. Therefore, the NMDA receptor hypoactivity hypothesized in schizophrenia may be attributable, in part, to disturbance of AMPA receptor expression or function. This is supported by decreases in AMPA receptor subunit mRNA and protein levels and [3H]CNQX binding in temporal cortex (Kerwin et al. 1990; Harrison et al. 1991; Eastwood et al. 1995; Eastwood et al. 1997a,b). However, little is known about the role of AMPA receptor expression in prefrontal cortex and striatum in schizophrenia.

To address this possibility, we examined AMPA receptor binding and subunit mRNA levels in prefrontal cortical and striatal regions of schizophrenics and matched controls to determine if AMPA receptor expression is altered in this illness. Our hypothesis was that AMPA receptor expression would be changed in limbic-associated prefrontal cortical and/or striatal regions, and any alterations in receptor expression would be detectable at the levels of mRNA expression and/or receptor binding.

## METHODS

### Subjects

Sixteen subjects with schizophrenia and nine controls were used in this study. These identical subjects have been studied in a previous report on dopamine receptor transcript expression (Meador-Woodruff et al. 1997). Clinical characteristics of these subjects were described in this earlier report and are summarized in Table 1. Because prior neuroleptic exposure can be a significant confound in postmortem studies, the schizophrenic group was subdivided into medicated and medication-free groups. The medication-free group consisted of six subjects who were off antipsychotics for at least 6 weeks prior to death. At autopsy, the subjects' brains were removed and one hemisphere was examined by a neuropathologist. There was evidence of significant neuropathology in two of the schizophrenics (cerebral infarcts in regions that we did not study) but none in the controls. The other hemisphere was dissected into blocks containing prefrontal cortex, occipital cortex, and striatum, and these blocks were rapidly frozen and stored at −80°C until they were cryostat sectioned (Meador-Woodruff et al.). Prefrontal cortical blocks contained Brodmann areas 9, 11, 32, and 46, although in several cases, all four areas were not available for analysis. Occipital cortical blocks contained Brodmann area 17. Striatal blocks contained rostral caudate, putamen, and nucleus accumbens, although blocks from 12 of the subjects did not contain nucleus accumbens, because the blocks were slightly more caudal than the accumbens.

### In Situ Hybridization

*In situ* hybridization for the transcripts encoding the AMPA receptor subunits was performed as previously described (Healy et al. 1997). Briefly, probes for each subunit were generated from subclones of each subunit, as shown in Table 2. Each subclone corresponds to coding regions common to all known splice variants and edited forms (Hollmann and Heinemann 1994), so each probe hybridized to the total pool of gluR1-gluR4 mRNA, respectively. After sections were fixed, acetylated, and dehydrated, 2–8 $\times$ $10^6$ dpm of probe were added to each section and incubated overnight. The next day, coverslips were removed, sections were treated with RNase, and washed in solutions with increasing stringencies. Sections were dehydrated and apposed to film Kodak XAR-5 for 1 to 4 weeks.

**Table 1.** Characterization of Subjects

| Subject # | Age (Years) | Gender | PMI (Minutes) | Cause of Death |
|---|---|---|---|---|
| Controls | | | | |
| 46 | 88 | M | 285 | Cardiac |
| 82 | 86 | F | 280 | Unknown |
| 93 | 70 | M | 482 | Pulmonary hypertension |
| 97 | 55 | M | 600 | Cancer |
| 192 | 79 | F | 181 | Cardiopulmonary failure |
| 230 | 96 | F | 195 | Cardiopulmonary failure |
| 231 | 90 | F | 250 | Cardiopulmonary failure |
| 232 | 74 | F | 180 | Cardiopulmonary failure |
| 361 | 98 | F | 85 | Cardiac |
| means ± SD | | 81.8 ± 13.8 | | 282.0 ± 161.7 |
| Schizophrenics (medicated) | | | | |
| 123 | 54 | M | 490 | Acute myelocytic leukemia |
| 190 | 61 | M | 212 | Cardiopulmonary failure |
| 195 | 69 | M | 270 | Cardiac infarction, renal failure |
| 199 | 76 | F | 510 | Cardiopulmonary failure, breast cancer |
| 212 | 75 | F | 334 | Cardiopulmonary failure |
| 331 | 63 | M | 372 | Cardiopulmonary failure |
| 337 | 69 | F | 820 | Cardiopulmonary failure |
| 338 | 87 | M | 670 | Cardiopulmonary failure |
| 356 | 68 | M | 335 | Cardiopulmonary failure |
| 363 | 64 | F | 392 | Cardiopulmonary failure |
| means ± SD | | 68.6 ± 9.2 | | 440.5 ± 187.0 |
| Schizophrenics (antipsychotic-free) | | | | |
| 106 | 86 | F | 415 | Respiratory insufficiency, renal failure |
| 172 | 86 | F | 330 | Cardiac, pneumonia |
| 193 | 84 | M | 372 | Cardiopulmonary failure |
| 257 | 72 | M | 1235 | Cardiopulmonary failure |
| 309 | 65 | F | 350 | Cardiopulmonary failure |
| 426 | 79 | F | 1225 | Cardiopulmonary failure, pancreatic cancer |
| means ± SD | | 78.7 ± 8.6 | | 652.8 ± 448.1 |

## Receptor Autoradiography

Slides were removed from −80°C and thawed at room temperature for 15 minutes. Slides were then soaked in 50 mm Tris-Citrate buffer (pH 7.4) at 4°C for 30 minutes to remove endogenous glutamate. The slides were quickly rinsed in water and dried with a hair dryer on cool setting. [$^3$H]AMPA was diluted in 50 mM Tris-Citrate, 100 mm KSCN buffer (pH 7.4) to a final concentration of 6 nm. This concentration was three times the $K_d$ we determined for [$^3$H]AMPA in human brain in a separate experiment. For each subject, two sections were incubated with [$^3$H]AMPA, while one section was incubated with [$^3$H]AMPA plus 1mM CNQX to determine nonspecific binding. After incubating for 45 minutes at 4°C, sections were quickly dipped in 50 mm Tris-Citrate buffer (pH 7.4) washed three times at 4°C, followed by one wash in water for 5 seconds. The slides were then dried with a hair dryer on cool setting. Slides were apposed to Amersham [$^3$H]Hyperfilm for eight weeks.

## Image Analysis

Images were acquired and stored by digitizing film images with a Macintosh-based CCD imaging system. Image analysis was performed using NIH Image 1.53. For *in situ* hybridization images, gray scale values were obtained from striatal regions and infragranular and su-

**Table 2.** Riboprobes Used for *in Situ* Hybridization

| Subunit | Subclone Length (Bases) | Corresponding Region (Relative to Coding Region) | | |
|---|---|---|---|---|
| gluR1 | 507 | −250 | to | 256 |
| gluR2 | 534 | 447 | to | 981 |
| gluR3 | 506 | −233 | to | 273 |
| gluR4 | 358 | −160 | to | 197 |

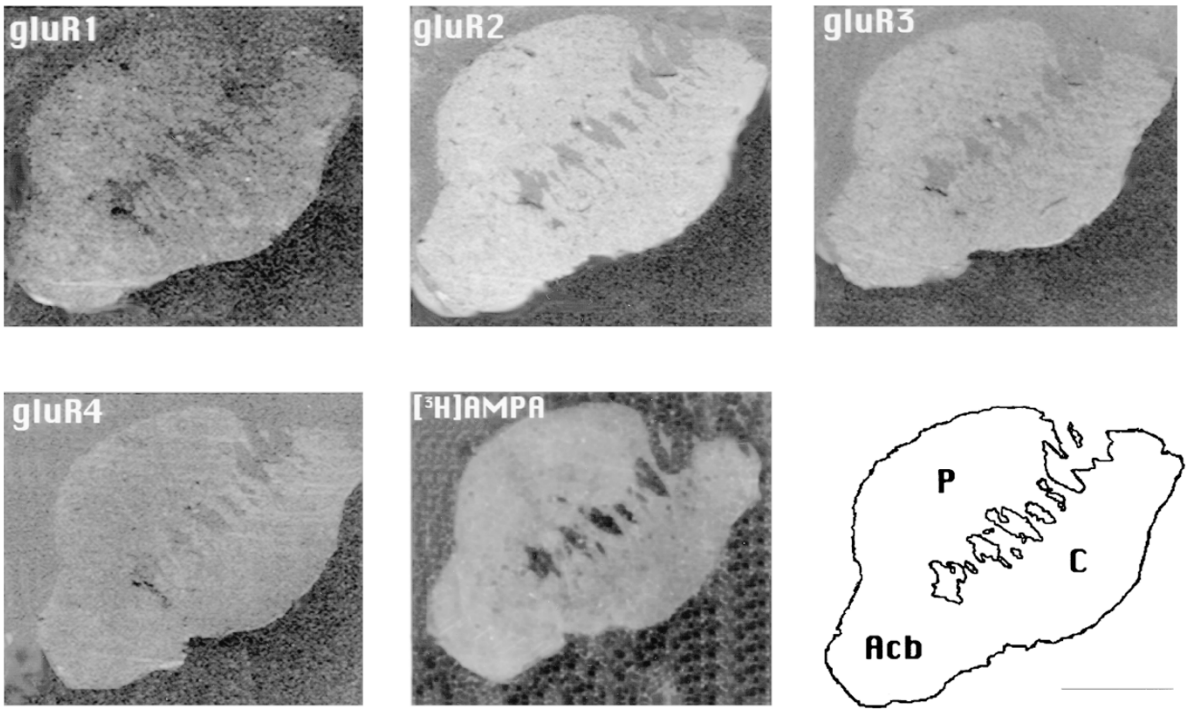


**Figure 1.** Distribution of AMPA receptor subunit mRNA levels and [$^3$H]AMPA binding in human striatum. Bar = 1 cm C = caudate nucleus; P = putamen; Acb = nucleus accumbens.

pragranular cortical laminae, corrected for tissue background, and converted to optical density. These values have been determined to be linear with concentration over the gray scale values found in this study. Values from two sections for each subject were averaged and used for subsequent data analysis. For receptor binding images, gray scale values were corrected for nonspecific binding, and converted to optical density. Values from two sections per subject were averaged and used for subsequent data analysis.

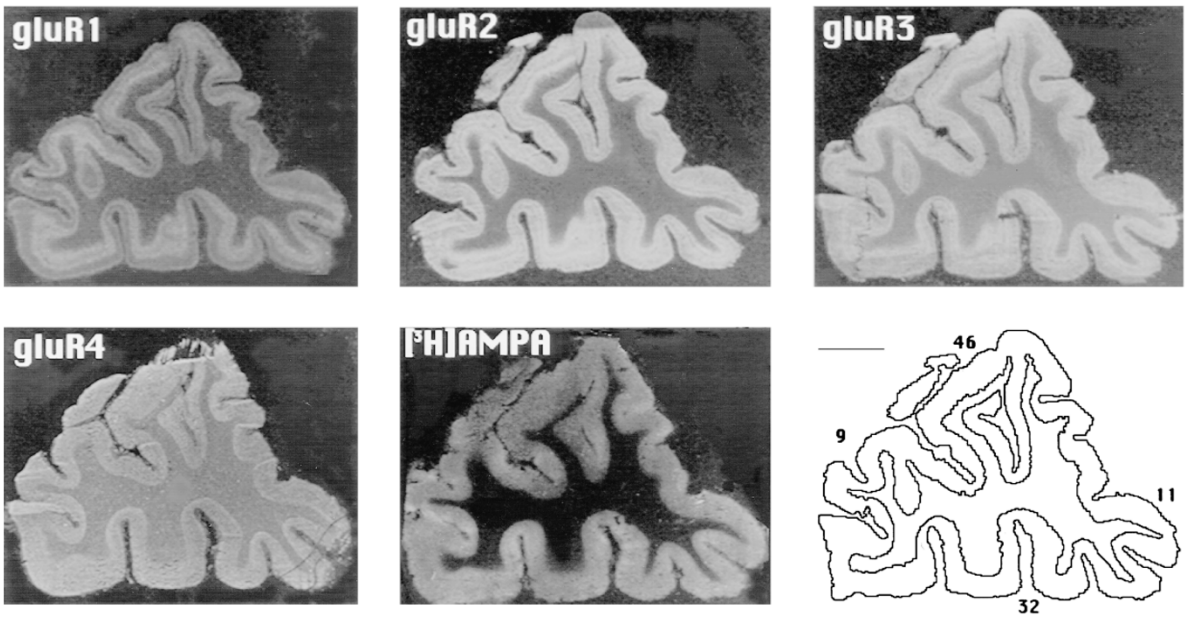


**Figure 2.** Distribution of AMPA receptor subunit mRNA levels and [$^3$H]AMPA binding in human cortex. Bar = 1 cm 9 = Brodmann area (BA) 9; 11 = BA 11; 32 = BA 32; 46 = BA 46.

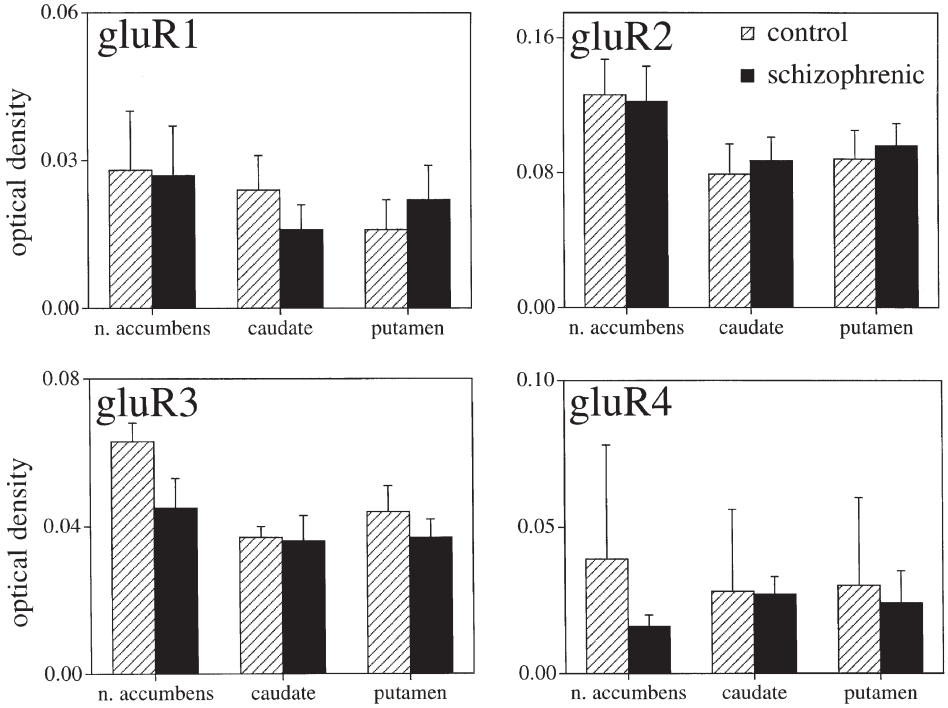


**Figure 3.** AMPA receptor subunit gluR1-gluR4 mRNA levels in striatum of schizophrenics and controls, expressed as mean ± sem. There were no statistically significant differences for diagnosis for any of the four subunit mRNA levels (gluR1: F(diagnosis) = .588; gluR2: F(diagnosis) = .961; gluR3: F(diagnosis) = .642; gluR4: F(diagnosis) = .359), nor were there any significant interactions between diagnosis and region. There was a main effect for region for gluR2 (F(region) = 23.0, $p < .00001$) and gluR3 (F(region) = 6.73, $p < .01$) mRNA levels.

### Statistical Analysis

Data were analyzed by multivariate analyses of covariance (MANCOVAs) for each region. In prefrontal cortex, 3 × 2 MANCOVAs were performed for each probe, with diagnosis, Brodmann area, and lamina included as independent variables. 2 × 2 MANCOVA analysis was performed for occipital cortex, with diagnosis and lamina as the independent variables. 2 × 2 MANCOVA analyses were performed for striatal regions, with the independent variables being diagnosis and subregion (caudate, putamen, and nucleus accumbens). Age and pmi covariates were included for all analyses. Separate analyses were performed to assess the putative effect of antipsychotic treatment on AMPA receptor expression, with medication status replacing diagnosis in all of the above analyses.

## RESULTS

All four AMPA receptor subunit transcripts were present in both cortex and striatum, as previously reported (Tomiyama et al. 1997) (Figures 1 and 2). Appreciable AMPA binding was also present in the cortex and striatum (Freed et al. 1993; Kurumaji et al. 1992; Noga et al. 1997) (Figure 1 and Figure 2). AMPA receptor subunit mRNA levels in striatal or cortical regions did not differ between controls and schizophrenics (Figure 3, Figure 5, and Figure 7). Likewise, schizophrenics displayed no difference from controls in AMPA receptor binding in cortical or striatal regions (Figure 4, Figure 6, and Figure 8). As is discussed in Meador-Woodruff et al. (1997), the controls had significantly shorter pmis than the schizophrenics and were older than the schizophrenics, although this difference was not statistically significant. When control subject #361 (who is an outlier for both age and pmi) is removed from the analysis, differences in either age or pmi are not significant between the two groups. None of the measures of AMPA receptor expression are altered by the deletion of subject #361.

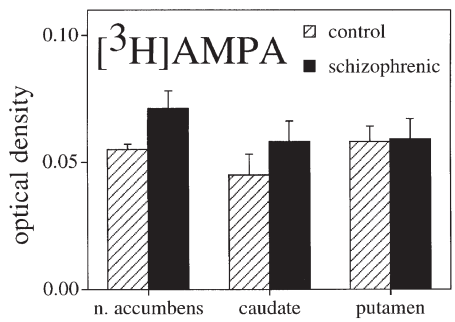


**Figure 4.** AMPA receptor binding levels in striatum of schizophrenics and controls, expressed as mean ± sem. There was no statistically significant effect of diagnosis or region on binding levels (F(diagnosis) = .380), nor was there any significant interaction term.

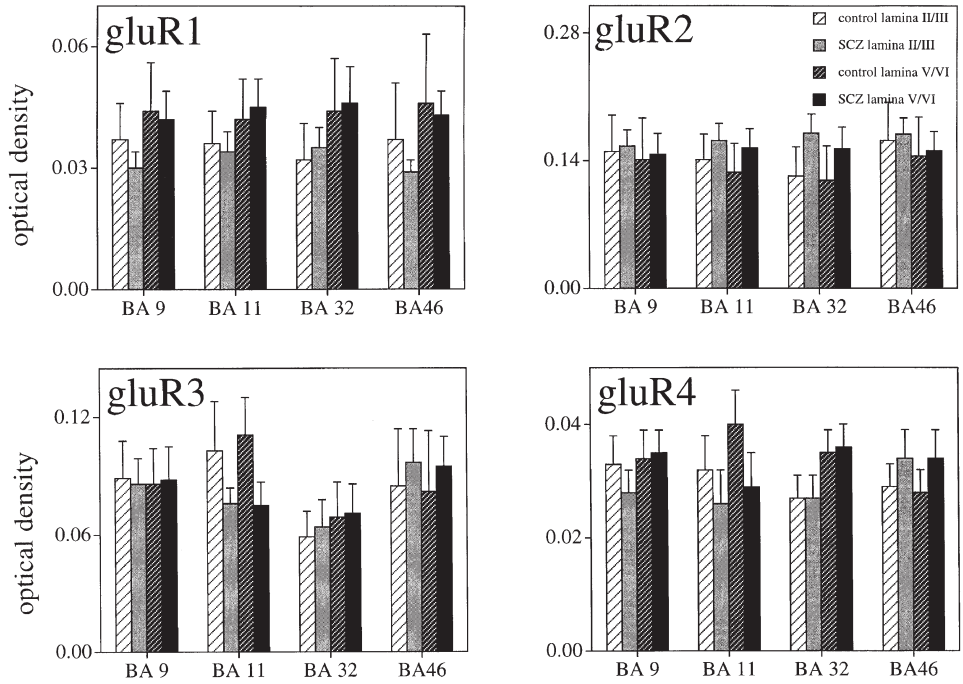


**Figure 5.** AMPA receptor subunit gluR1-gluR4 mRNA levels in frontal cortical regions of schizophrenics and controls, expressed as mean ± sem. There were no statistically significant differences for diagnosis for any of the four subunit mRNA levels (gluR1: F(diagnosis) = .700; gluR2: F(diagnosis) = .918; gluR3: F(diagnosis) = .003; gluR4: F(diagnosis) = .359), nor were there any significant interactions between diagnosis, lamina, and Brodmann area except a diagnosis × Brodmann area interaction for gluR3 (F(diagnosis × Brodmann area) = 2.79, $p < .05$) and a Brodmann area × lamina interaction for gluR4 (F (Brodmann area × lamina) = 4.24, $p < .005$). There was a main effect for lamina for gluR1 (F(lamina) = 7.24, $p < .05$), gluR2 (F(lamina) = 5.43, $p < .05$) and gluR4 (F(lamina) = 7.91, $p < .05$) mRNA levels.

To determine if chronic antipsychotic exposure affects expression of these receptor molecules, schizophrenics were subdivided into unmedicated and medicated groups, and these data were reanalyzed. Neither subgroup displayed significant differences with the control group or with each other (data not shown).

## DISCUSSION

There were no significant differences in AMPA receptor expression in either cortical or striatal regions. This is in agreement with a previous study that found no changes in AMPA binding in these same prefrontal cortical areas (Kurumaji et al. 1992), and a separate study that found no changes in AMPA binding in caudate of schizophrenics (Freed et al. 1993). Another study (Noga et al. 1997) demonstrated an increase in [$^3$H]CNQX binding, which the authors propose is specific for AMPA receptors. Different methodologies, and the different ages of the populations under study, may account for this discrepancy. However, our study is the first study to measure AMPA receptor subunit mRNA levels in cortex and striatum in schizophrenia, and to measure both AMPA receptor binding and subunit mRNA levels in these regions in the same subjects.

Previous studies of AMPA receptor expression have focused on the temporal lobe. Kerwin et al. (1990) found a decrease in hippocampal quisqualate binding

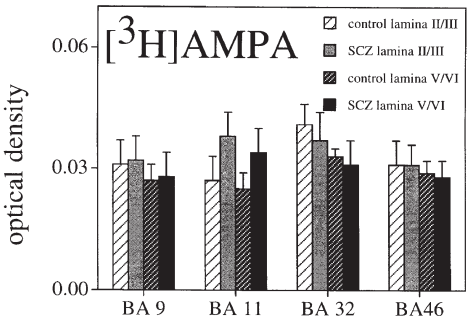


**Figure 6.** AMPA receptor binding levels in frontal cortical regions of schizophrenics and controls, expressed as mean ± sem. There was no statistically significant effect for diagnosis on binding levels (F(diagnosis) = .011), nor were there any significant interactions between diagnosis, Brodmann area, and lamina. There was a main effect for lamina for AMPA binding levels (F(lamina) = 19.0, $p < .0005$).

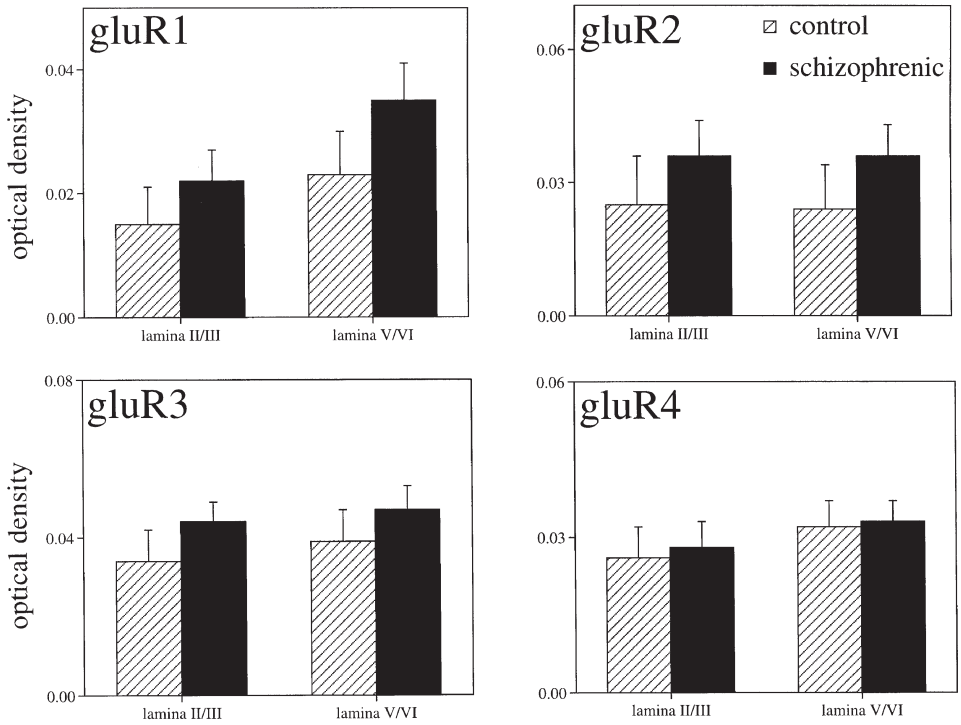


**Figure 7.** AMPA receptor subunit gluR1-gluR4 mRNA levels in occipital cortex of schizophrenics and controls, expressed as mean ± sem. There were no statistically significant differences for diagnosis for any of the four subunit mRNA levels (gluR1: F(diagnosis) = .190; gluR2: F(diagnosis) = .380; gluR3: F(diagnosis) = .285; gluR4: F(diagnosis) = .056), nor were there any significant interactions between diagnosis and region. There was a main effect for lamina for gluR1 (F(lamina) = 10.2, $p < .005$), gluR3 (F(lamina) = 7.98, $p < .01$), and gluR4 (F(diagnosis) = 6.49, $p < .05$) mRNA levels.

in schizophrenics, and the same group found decreased expression of gluR1 and gluR2 mRNA levels in hippocampus, and decreased gluR2 mRNA levels in parahippocampal gyrus (Harrison et al. 1991; Eastwood et al. 1995). Concomitant decreases in gluR1 and gluR2/3 immunoreactivity were also significant, but less striking (Eastwood et al. 1997b). Conversely, Breese et al. (1995) found no change in gluR1-gluR3 immunoreactivity in hippocampus or cingulate cortex, although, interestingly, patients with a history of alcohol abuse had increased gluR2 and gluR3 immunoreactivity levels.

Although receptor binding and mRNA levels were not altered in schizophrenia in our study, this does not completely eliminate a role for AMPA receptor dysfunction in schizophrenia. AMPA receptor function depends upon the functional properties conferred by differing subunit composition (Hollmann et al. 1991; Burnashev et al. 1992), and this study does not measure these functional properties. Furthermore, each subunit has splice variants, with differing properties, but we measured total gluR1-gluR4 mRNA levels. An imbalance in processing mRNA, without a change in total mRNA levels, may potentially cause AMPA receptor dysfunction, but our study could not address this possibility. Consistent with this idea is a study that found a decrease in both the flip and flop isoforms of gluR2 mRNA levels in hippocampal formation (Eastwood et al. 1997a). The decrease in the flop isoform was greater than for the flip, so that the flip:flop ratio increased by 25% (Eastwood et al. 1997a). This change in mRNA processing in schizophrenics, for the only subunit mRNA examined, suggests that the function of AMPA receptors may be altered in schizophrenia because of the presence of different isoforms of subunits in the final receptors.

AMPA receptor expression was not altered by antipsychotic treatment in our subjects, which contradicts preclinical studies in rodents that suggest that clozapine and haloperidol treatment alter AMPA receptor subunit mRNA levels and [$^3$H]AMPA binding in cortex and striatum. One study demonstrated that haloperidol

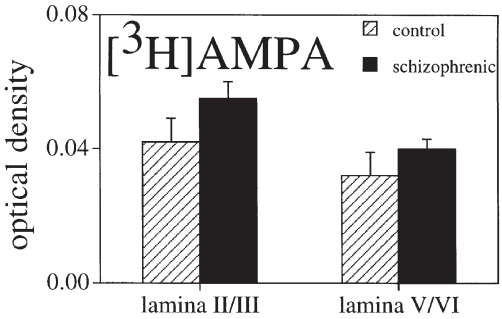


**Figure 8.** AMPA receptor binding levels in occipital cortex of schizophrenics and controls, expressed as mean ± sem. There was no statistically significant effect for diagnosis on binding levels (F(diagnosis) = .952), nor was there any significant interaction between diagnosis and lamina. There was a main effect for lamina for AMPA receptor binding (F(lamina) = 27.7, $p < .00005$).

caused a decrease in gluR2 and gluR4 mRNA levels in both cortex and striatum, whereas, clozapine treatment caused a decrease in gluR3 mRNA expression in both cortex and striatum, and a decrease in gluR4 mRNA levels in the striatum (Healy et al. 1997). In another study, haloperidol treatment did not alter gluR1 mRNA levels but did alter gluR2 mRNA processing (increase in flip:flop ratio) in striatum and frontal cortex (Eastwood et al. 1996). [$^3$H]AMPA binding was increased by 21 day haloperidol, but not clozapine, treatment in frontal cortex and striatum (McCoy et al. 1996), whereas, [$^3$H]CNQX binding was unaffected by either treatment (McCoy et al.; Tarazi et al. 1996). Fitzgerald et al. (1995) found increases in gluR1 immunoreactivity in rat striatum and frontal cortex after haloperidol and clozapine treatment, whereas, clozapine treatment also increased gluR2 immunoreactivity in frontal cortex and nucleus accumbens. These studies demonstrated the effects of antipsychotic treatment on the AMPA receptor at three levels of expression (mRNA, protein, and binding) in rat, suggesting a species difference in antipsychotic regulation of AMPA receptor expression. The disparity between these rodent and our present human data underscores the need for caution in attempting to apply data from rodent studies in the interpretation of data derived from human studies.

This study presents a large number of negative results, and the risk of Type II error must be considered. Therefore, we performed "reverse power calculations." For occipital cortical mRNA and binding levels, we estimate that a difference of 18% would have been found to be statistically significant, whereas, for prefrontal cortical mRNA and binding levels, a 12% difference between groups would be statistically significant. Significant differences of 19% or more would be detected for striatal mRNA and binding levels. Although changes of less than 10 to 15% would not be found in the present study, we feel fairly confident that there is a low risk for Type II error.

In conclusion, our data do not support a role for altered AMPA receptor binding and subunit mRNA levels in the cortex and striatum of elderly schizophrenics, nor do these levels seem to be affected by antipsychotic treatment.

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