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Letters to the Editors

AMPA receptor binding in the dorsolateral prefrontal cortex of schizophrenics and controls

To the Editors

Hypothesizing elevated AMPA receptor concentration in the primarily receptive (i.e. superficial) layers of dorsolateral prefrontal cortex (DLPFC) in schizophrenia, we examined [^3H]CNQX (AMPA receptor), [^3H]MK801 (NMDA receptor), [^3H]KA (kainic acid receptor), and [^3H]D-aspartate (D-Asp) binding in the post-mortem DLPFC (Brodmann area 46) of six (DSM-III-R) schizophrenics [mean age \pm S.D. 56.8 ± 16.3 years; 4 female, 2 male; post-mortem interval (PMI) 21.8 ± 8.7 h], nine normal controls (mean age \pm SD 54.8 ± 15.5 ; 3 female, 6 male; PMI 25.5 ± 13.6), four non-schizophrenic neuroleptic-treated controls (mean age 55.1 ± 19.3 ; 1 female, 3 male; PMI 32.6 ± 22.2), and nine nonpsychotic suicide victims (mean age 57.2 ± 23.9 ; 2 female, 7 male; PMI 27.0 ± 10.7) using quantitative autoradiographic methods on slide-mounted frozen sections (Noga et al., 1997). Mean age and PMI did not differ statistically among groups (ANOVA $P > 0.1$). Six cortical laminae were reliably measured for [^3H]CNQX and [^3H]D-Asp binding, but only layers 1/2, 3/4, and 5/6 for [^3H]MK801 (NMDA receptor) and [^3H]KA. Reliability on different days (by author T.M.H.) exceeded 0.90 (intraclass coefficient). Student's t -test (one-tailed) was used to test the specific hypothesis of elevated [^3H]CNQX binding in schizophrenics relative to normals. Two-tailed t -tests or analysis of variance were used for comparisons not related to the hypothesis.

[^3H]CNQX binding was greater in schizophrenics than in normal controls in every layer (see Table 1 and Fig. 1), reaching significance in layer 2 ($P = 0.036$). The schizophrenic group was also elevated with respect to suicides ($P = 0.04$, layer 2) and neurolep-

tic-treated controls ($P < 0.04$, layers 2, 3, 4, and 5). Suicides did not differ significantly from normal controls in any cortical layer ($P > 0.1$). ANOVA main effects for [^3H]KA, [^3H]MK801, and [^3H]D-Asp binding were not significant ($P > 0.1$).

Increased [^3H]CNQX binding in the schizophrenics is not readily attributable to the effect of antipsychotic drugs because the neuroleptic-treated controls exhibited lower [^3H]CNQX binding than the normal controls (i.e. opposite the direction of the schizophrenics from normals) in all laminae, and because the increase in the schizophrenia group reached significance only in lamina 2. This result is not consistent with that of Healy et al. (1998), who found no difference in [^3H]AMPA binding or GluR1–4 mRNA expression in layers 2/3 and 5/6 of prefrontal cortex in areas 46, 32, 9, or 11; however, the mean ages of their schizophrenics and normals was more than 10 years greater than those of our sample. Although the suggestion of increased DLPFC AMPA receptor concentration in schizophrenia is regarded as preliminary, recognizing limitations due to the small sample size, neuroleptic exposure, and the broad nature of the hypothesis, it may be relevant to pathophysiological processes in schizophrenia, particularly cortical dysfunction. The superficial cortical laminae are important terminal fields in cortico-cortical signaling and rich in AMPA receptors. AMPA receptors are of particular interest because of their potential role in the regulation of prefrontal dopamine release under stress conditions in nonhuman primates (Jedema and Moghaddam, 1994; Maione et al., 1995), their importance in synaptic plasticity (memory, ontogenesis, and response to neural injury), and as potential therapeutic targets for AMPA agonists in the treatment of schizophrenia (Staubli et al., 1994; Arai et al., 1996; Sirvio et al., 1996; Goff et al., 1999; Johnson et al., 1999). The data are presented to stimulate further interest in AMPA glutamate receptors in relation to cortical signaling in schizophrenia.

Table 1

Mean binding densities (fmol/mg \pm standard deviation)

PFC layer	Schizophrenics	Normals	Neuroleptic controls	Suicides
$[^3\text{H}]\text{CNQX}$				
Layer 1	3.8 \pm 0.9	3.0 \pm 1.1	1.5 \pm 1.5	3.0 \pm 1.4
Layer 2	8.7 \pm 1.2	7.5 \pm 1.2	4.3 \pm 2.0	6.7 \pm 1.9
Layer 3	9.0 \pm 1.8	8.1 \pm 1.2	5.4 \pm 2.7	8.6 \pm 2.7
Layer 4	7.9 \pm 1.3	7.4 \pm 0.7	4.6 \pm 1.8	7.8 \pm 1.9
Layer 5	8.2 \pm 1.5	7.7 \pm 0.6	4.8 \pm 1.8	8.0 \pm 1.8
Layer 6	5.4 \pm 1.2	4.9 \pm 1.3	3.6 \pm 1.6	5.1 \pm 1.6
$[^3\text{H}]\text{Kainic acid}$				
Layer 1/2	34.5 \pm 6.9	37.7 \pm 5.4	42.7 \pm 2.9	37.3 \pm 7.5
Layer 3/4	34.0 \pm 4.9	40.4 \pm 5.5	45.0 \pm 4.4	40.2 \pm 7.5
Layer 5/6	50.7 \pm 11.2	55.8 \pm 11.6	65.7 \pm 6.4	57.0 \pm 8.3
$[^3\text{H}]\text{MK801}$				
Layer 1/2	0.30 \pm 0.29	0.48 \pm 0.29	0.55 \pm 0.14	0.33 \pm 0.26
Layer 3/4	0.37 \pm 0.27	0.58 \pm 0.27	0.54 \pm 0.45	0.58 \pm 0.32
Layer 5/6	0.27 \pm 0.14	0.43 \pm 0.27	0.37 \pm 0.48	0.32 \pm 0.24
$[^3\text{H}]\text{D-Aspartic acid}$				
Layer 1	13.1 \pm 5.7	12.2 \pm 4.7	11.2 \pm 3.7	14.5 \pm 4.1
Layer 2	19.9 \pm 5.9	20.2 \pm 5.8	15.4 \pm 8.8	21.6 \pm 6.2
Layer 3	20.0 \pm 4.8	19.2 \pm 4.6	15.1 \pm 10.5	18.7 \pm 5.3
Layer 4	15.9 \pm 2.9	15.0 \pm 3.7	13.9 \pm 9.4	16.1 \pm 5.2
Layer 5	14.5 \pm 4.5	14.0 \pm 3.0	13.7 \pm 8.5	15.3 \pm 4.8
Layer 6	9.9 \pm 3.8	9.5 \pm 2.0	9.2 \pm 5.0	11.8 \pm 3.3

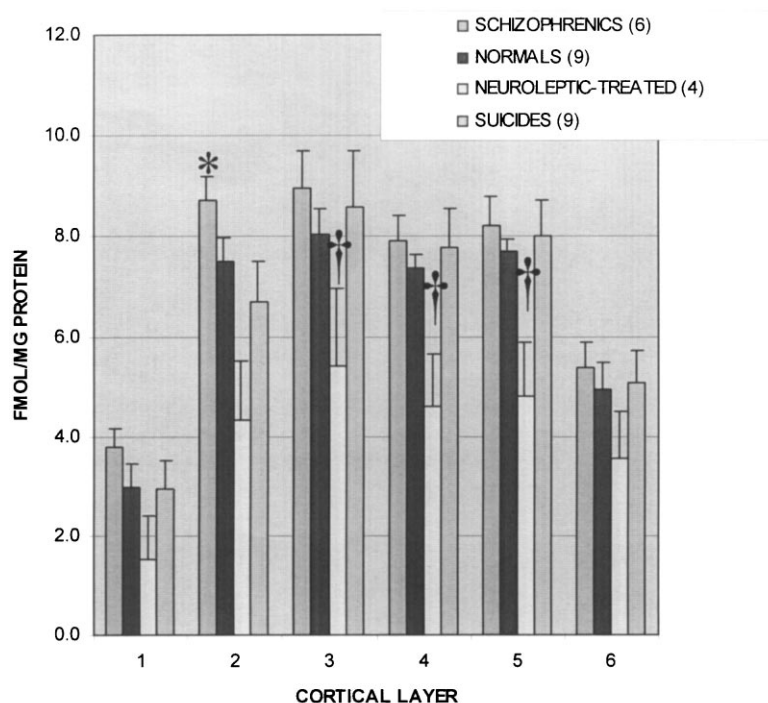


Fig. 1. $[^3\text{H}]\text{CNQX}$ binding in DLPFC. *Layer 2: schizophrenics > normal controls ($P = 0.035$, one-tailed), suicides ($P = 0.04$, two-tailed), and neuroleptic controls ($P < 0.003$, two-tailed); normals > neuroleptic controls ($P = 0.004$, two-tailed). †Layers 3, 4, and 5: neuroleptic-treated controls < normals ($P < 0.03$, two-tailed) and schizophrenics ($P < 0.04$, two-tailed).

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HLA-A2 and B35 are strong predictors of responsiveness to clozapine: preliminary data in Italian schizophrenic patients

Dear Sir

It has recently been suggested that the individual susceptibility to develop agranulocytosis and the patients' responsiveness to clozapine are both Human Leukocyte Antigen (HLA) associated (Valevski et al., 1998).

To the best of our knowledge, up to now only one study has investigated the role of the HLA region in clozapine responsiveness (Lahdelma et al., 1998); results of this study showed an association with an HLA-A antigen.

The study below was designed to re-examine the role of HLA antigens in influencing the clinical outcome of clozapine treatment in schizophrenic patients.

Thirty-one Italian schizophrenic outpatients were enrolled after giving their consent to participate in the study. DSM-IV (American Psychiatric Association, 1994) criteria and Kane criteria (Kane et al., 1988) were employed, respectively, for psychiatric diagnosis and for the definition of resistance to neuroleptic treatment. Clinical and demographic characteristics of the study population are summarised below:

1. *high clozapine responders* ($n = 19$): male 63%, age 36 ± 2 years (mean \pm S.E.M.), age at onset 24 ± 2 years (mean \pm S.E.M.), length of illness 12 ± 2 years (mean \pm S.E.M.), level of education 10 ± 1 years (mean \pm S.E.M.), clozapine dosage 355 ± 30 mg (mean \pm S.E.M.), BPRS score at T_0 72 ± 4 (mean \pm S.E.M.), BPRS score at T_1 23 ± 1 (mean \pm S.E.M.).
2. *medium-low clozapine responders* ($n = 12$): male 92%, age 30 ± 2 years (mean \pm S.E.M.), age at onset 22 ± 1 years (mean \pm S.E.M.), length of illness 8 ± 2 years (mean \pm S.E.M.), level of education 10 ± 1 years (mean \pm S.E.M.), clozapine dosage 508 ± 39 mg (mean \pm S.E.M.), BPRS score at T_0 66 ± 4 (mean \pm S.E.M.), BPRS score at T_1 47 ± 3 (mean \pm S.E.M.).

All the patients were administered clozapine for 8 months. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used to