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Reply to Balcar and Nanitsos

Reply: Autoradiography of [^{3}H]aspartate and Glutamate Transport in Schizophrenia

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Sir

We would like to respond to issues raised by Balcar and Nanitsos on our study of cortical glutamatergic markers in schizophrenia (Scarr *et al*, 2005). Before addressing the issue raised by Balcar and Nanitsos, we would first emphasize that their comments only focus on a small component of our paper without acknowledging that we have completed a comprehensive study of cortical glutamatergic markers in schizophrenia. Moreover, they do not mention that the data from our study strongly supports the hypothesis that the density of the kainate receptor is decreased across the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia and that this decrease appears to be associated with a decrease in the expression of the GluR5, but not GluR6, GluR7, KA1 or KA2, subunit of the kainate receptor. In addition, our radioligand binding data did not support the notion that the density of the *N*-methyl D-aspartate (NMDA) receptor, measured using two radioligands directed at two discrete sites of the NMDA receptor, or the amino-3-hydroxyl-5-methyl-4-isoxazole (AMPA) receptor is altered in subjects with the disorder.

Turning to the issue of the interpretation of our data on [^{3}H]aspartate binding raised by Balcar and Nanitsos. First of all we must correct the statement made by these authors as we did not, as they suggest, claim that 'glutamate transport in cortical areas affected by schizophrenia is not changed'. In fact, a careful reading of the discussion of our paper reveals that we limited the interpretation of our data to suggesting 'there is no change in the levels of high-affinity glutamate uptake sites in the DLPFC with schizophrenia'. The term 'high-affinity glutamate uptake sites' was used to define sites in the human cortex that bind [^{3}H]aspartate with high affinity and show pharmacological characteristics of a glutamate uptake site (Cross *et al*, 1986). In the absence of more defining data, such as the measurement of transcripts for the different glutamate transporters, our binding data could not be interpreted further. Thus, from our perspective, Balcar and Nanitsos have overinterpreted both the molecular and the anatomical extent (we did not make a statement on the entire human cortex) of our comments on [^{3}H]aspartate binding.

On the broader issue raised by Balcar and Nanitsos that glutamate transport may be affected in schizophrenia, we are aware of many postmortem studies that would support this hypothesis. For example, while early membrane binding studies failed to show changes in [^{3}H]aspartate binding in the prefrontal cortex, they did report changes in binding in other cortical and subcortical regions from subjects with schizophrenia (Deakin *et al*, 1989; Aparicio-Legarza *et al*, 1997). In addition, members of our group suggest that there are changes in the expression and activity of enzymes in the glutamate/glycine cycle (Bruneau *et al*, 2005) and expression of the excitatory amino acid transporters (EAAT) 1–3 (McCullumsmith *et al*, 2004; McCullumsmith and Meador-Woodruff 2002) in schizophrenia. Such data add to findings that suggest that changes in EAATs are present in CNS regions, such as the cortex (Ohnuma *et al*, 1998), striatum (McCullumsmith and Meador-Woodruff 2002), thalamus (Smith *et al*, 2001a), and hippocampal formation (Ohnuma *et al*, 2000), from subjects with schizophrenia. Moreover, aberrations in glutamatergic function may also result from changes in glutamate uptake by glia (Glt-1 transporter) (Matute *et al*, 2005) or because of changes in vesicular glutamate transporter (Eastwood and Harrison, 2005; Smith *et al*, 2001b) in different CNS regions from subjects with schizophrenia. On addressing the issue of changes in glutamate uptake by glia, Balcar and Nanitsos suggest that increased levels of EAATs have been reported in

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postmortem schizophrenic brains from nonmedicated patients (Matute *et al*, 2005). This statement is a little misleading and not carefully defined. The study cited was completed using postmortem CNS from 11 subjects with schizophrenia, 8 of whom were medicated and three of whom 'had not received antipsychotic drugs for an amount of time' before death, only two of which were used for expression studies. The study showed that levels of mRNA for Glt-1 (Glt-1 = EAAT2) were increased in the medication-free subjects, not changed in tissue from subjects on atypical antipsychotic drugs at death ($n = 3$), and decreased in subjects on typical antipsychotic drugs at death ($n = 5$). What conclusions can be drawn from a study where cohorts for analyses consisted of five subjects or less is open to conjecture; however, the study does suggest that antipsychotic drug treatment may be a confounding factor in interpreting results on glutamate transporters in schizophrenia.

Given extensive data from the study of postmortem CNS from subjects with schizophrenia, we would not dispute the suggestion of Balcar and Nanitsos that it is premature to suggest that glutamate transport is not changed in the cortex of subjects with schizophrenia. Indeed, this is why we did not draw that conclusion in our study of glutamatergic markers in the cortex of subjects with the disorder (Scarr *et al*, 2005). However, we would suggest debate on a minor component of our study does not in any way detract from our data showing a decrease in the expression of the GluR5 subunit and decreased levels of [^{3}H]kainate binding in the DLPFC.

REFERENCES

Aparicio-Legarza MI, Cutts AJ, Davis B, Reynolds GP (1997). Deficits of [^{3}H]D-aspartate binding to glutamate uptake sites in striatal and accumbens tissue in patients with schizophrenia. *Neurosci Lett* **232**: 13–16.

Bruneau EG, McCullumsmith RE, Haroutunian V, Davis KL, Meador-Woodruff JH (2005). Increased expression of glutaminase and glutamine synthetase mRNA in the thalamus in schizophrenia. *Schizophr Res* **75**: 27–34.

Cross AJ, Skan WJ, Slater P (1986). The association of [^{3}H]D-aspartate binding and high-affinity glutamate uptake in the human brain. *Neurosci Lett* **63**: 121–124.

Deakin JF, Slater P, Simpson MD, Gilchrist AC, Skan WJ, Royston MC *et al* (1989). Frontal cortical and left temporal glutamatergic dysfunction in schizophrenia. *J Neurochem* **52**: 1781–1786.

Eastwood SL, Harrison PJ (2005). Decreased expression of vesicular glutamate transporter 1 and complexin II mRNAs in schizophrenia: further evidence for a synaptic pathology affecting glutamate neurons. *Schizophr Res* **73**: 159–172.

Matute C, Melone M, Vallejo-Illarramendi A, Conti F (2005). Increased expression of the astrocytic glutamate transporter GLT-1 in the prefrontal cortex of schizophrenics. *Glia* **49**: 451–455.

McCullumsmith RE, Gupta DS, Haroutunian V, Davis KL, Meador-Woodruff JH Expression of excitatory amino acid transporter 1–3 transcripts in the prefrontal cortex in schizoprhenia. Program No. 909.15. *2004 Abstract Viewer/Itinerary Planner*. Society for Neuroscience: Washington; 2004.

McCullumsmith RE, Meador-Woodruff JH (2002). Striatal excitatory amino acid transporter transcript expression in schizophrenia, bipolar disorder, and major depressive disorder. *Neuropsychopharmacology* **26**: 368–375.

Ohnuma T, Augood SJ, Arai H, McKenna PJ, Emson PC (1998). Expression of the human excitatory amino acid transporter 2 and metabotropic glutamate receptors 3 and 5 in the prefrontal cortex from normal individuals and patients with schizophrenia. *Brain Res Mol Brain Res* **56**: 207–217.

Ohnuma T, Tessler S, Arai H, Faull RL, McKenna PJ, Emson PC (2000). Gene expression of metabotropic glutamate receptor 5 and excitatory amino acid transporter 2 in the schizophrenic hippocampus. *Brain Res Mol Brain Res* **85**: 24–31.

Scarr E, Beneyto M, Meador-Woodruff JH, Dean B (2005). Cortical glutamatergic markers in schizophrenia. *Neuropsychopharmacology* **30**: 1521–1531.

Smith RE, Haroutunian V, Davis KL, Meador-Woodruff JH (2001a). Expression of excitatory amino acid transporter transcripts in the thalamus of subjects with schizophrenia. *Am J Psychiatry* **158**: 1393–1399.

Smith RE, Haroutunian V, Davis KL, Meador-Woodruff JH (2001b). Vesicular glutamate transporter transcript expression in the thalamus in schizophrenia. *NeuroReport* **12**: 2885–2887.