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Author/s:

Gibbons, AS;Brooks, L;Scarr, E;Dean, B

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AMPA receptor expression is increased in the anterior cingulate form subjects with major depressive disorder

Andrew Stuart Gibbons^{1,2}, Lucy Brooks^{1,4,5}, Elizabeth Scarr^{1,3}, Brian Dean^{1,2,6}

¹Rebecca L Cooper Laboratories, Mental Health Research Institute of Victoria, Parkville, Victoria, Victoria 3052, Australia.

²Department of Psychiatry, The University of Melbourne, Parkville, Victoria 3010, Australia.

³The Centre for Neuroscience, The University of Melbourne, Victoria Australia

⁴ Department of Anatomy and Cell Biology, The University of Melbourne, Parkville, Victoria 3010, Australia.

⁵Department of Neuroscience, The University of Nottingham, Nottingham, UK.

⁶Department of Psychological Medicine, Monash University, Clayton, Victoria 3800, Australia.

Abstract

Glutamate is thought to be involved in the pathophysiology of major depressive disorder and bipolar disorder, however, the molecular changes underlying abnormal glutamatergic signalling remain poorly understood. We sought to examine whether the expression of the non-NMDA, ionotropic glutamate receptors AMPA receptor and kainate receptor is altered in mood disorders. We used [³H]AMPA, [³H]kainate to measure the levels of AMPA receptor and kainate receptor, respectively, in BA 24, and BA 46 in the post-mortem CNS from 10 subjects with major depressive disorder, 10 subjects with bipolar disorder and 10 control subjects. [³H]AMPA binding density was increased in BA 24 ($p < 0.05$) but not BA 46 ($p > 0.05$) in major depressive disorder compared to control levels. [³H]AMPA binding density was not changed in bipolar disorder in either BA 24 or BA 46 ($p > 0.05$) compared to controls. [³H]Kainate binding was not changed in either BA 24 or BA 46 in either disorder compared to controls ($p > 0.05$). Our data is novel in showing an increase in AMPA receptor binding in the anterior cingulate of subjects with major depressive disorder. There was no evidence of abnormal non-NMDA receptor ionotropic glutamate receptor expression associated with bipolar disorder.

Keywords: AMPA Receptor, Kainate Receptor, Major Depressive Disorder, Bipolar Disorder Frontal Cortex

Correspondence:

Dr. Andrew Stuart Gibbons
The Rebecca L. Cooper Research Laboratories
The Mental Health Research Institute of Victoria
155 Oak Street,
Parkville, Victoria 3052, Australia
Email: a.gibbons@mhri.edu.au

Introduction

Glutamate, the major excitatory neurotransmitter in the cortex (McCormick, 1992; Tsumoto, 1990), has been implicated in the pathophysiology of mood disorders. The notion that abnormalities in glutamatergic abnormalities are involved in the pathophysiology of mood disorders was originally supported by the findings that glutamate levels are increased in the blood of patients with major depressive disorder (MDD) (Mauri et al., 1998). More recently it has been suggested that there is a positive correlation between plasma levels of glutamate and the severity of depressive symptoms (Mitani et al., 2006). In contrast to MDD, decreased plasma glutamate has been reported in patients with bipolar disorder (BPD) during their first psychotic episode, with pharmacotherapy (spell out the treatment ? antipsychotics) being capable of restoring glutamate to that found in control subjects (Palomero-Gallagher et al., 2009). In addition to peripheral studies, brain imaging studies have reported reduced glutamate levels in the anterior cingulate of subjects with MDD during depressive episodes (Auer et al., 2000) whilst a post mortem study report increased glutamate levels in the premotor cortex of subjects with MDD and BPD (Hashimoto et al., 2007).

Several reviews highlight suggest a role for the ionotropic N-methyl-D-aspartate receptor (NMDAR) in the pathophysiology of mood disorders (Javitt, 2004; Petrie et al., 2000; Skolnick et al., 2009). However, there appears to be little data on the possible involvement of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPA) and the kainate receptor in the pathophysiology of mood disorders. This is significant because animal studies suggest the AMPAR works in concert with NMDAR on the post-synaptic bouton to mediate glutamate's effect on mood (Maeng et al., 2008). Significantly, the AMPAR potentiator LY 392098 has been shown to improve performance on the forced swim test and tail suspension test in mice (Li et al., 2001; Li et al., 2003), both of which are thought to be indicative behaviours induced by manipulating sites that have potential antidepressant activity. Notably, the kainate receptor is thought to regulate glutamate release (Jouhannau et al., 2011). Thus, abnormal kainate receptor expression could have a considerable impact of glutamatergic neurotransmission. Post-mortem studies have reported decreased [³H]kainate binding in the dorsolateral prefrontal cortex and hippocampus from subjects with schizophrenia (Kerwin et al., 1988; Scarr et al., 2005). Comparable data on [³H]kainate

binding in the cortex of subjects with mood disorders is not available. However, mRNA expression of the kainate receptor GRIK5 subunit is decreased in MDD and BPD in the prefrontal cortex (BA 8, BA9, BA 10 and BA 46) (Knable et al., 2001) whereas the antidepressants fluvoxamine and imipramine have been shown to increase mRNA expression of kainate receptors (Havard et al., 1991). Together, these data suggest kainate receptor expression is affected in mood disorders.

Given the paucity of data on AMPAR and kainate receptors in the CNS of subjects with mood disorders, we sought to measure the binding of AMPAR and kainate receptor-selective radioligands in post-mortem CNS from subjects with MDD and BPD. Binding levels were measured in the dorsolateral prefrontal cortex (DLPFC) (Brodmann's Area [BA] 46) and the anterior cingulate (ACC) (BA 24), two regions highlighted by neuroimaging studies as being affected in mood disorders (Soares and Mann, 1997).

Methods

Tissue collection

Radioligand binding was performed on post-mortem cortical tissue from 10 subjects diagnosed with BPD, 10 subjects diagnosed with MDD and 10 subjects with no history of psychiatric illness (controls). All tissue was obtained from the Victorian Brain Bank Network and approval was obtained from both the Ethics Committee of the Victorian Institute of Forensic Medicine and the Mental Health Research and Ethics Committee of Melbourne Health. For each subject, a psychologist and psychiatrist reached a diagnostic consensus according to DSM-IV criteria (Hill et al., 1996; Roberts et al., 1998) following an extensive case history review using the Diagnostic Instrument for Brain Studies (DIBS) (Keks et al., 1999). The age, gender, post-mortem interval (PMI) and CNS pH of the subjects is outlined in *Table 1*. Cadavers were refrigerated within 5 hr and tissue was frozen to -70°C within 30 min of autopsy. Where death was witnessed, the time between death and autopsy was taken as the post-mortem interval (PMI). Where death was not witnessed, tissue was only collected from subjects who had been seen alive up to 5 hr prior to being found dead. In such cases, PMI was measured from the midpoint between the subject being found and being last seen alive. The pH of the CNS was measured as described previously (Kingsbury et al., 1995).

Tissue from Brodmann's Area (BA) 24 and BA 46 was dissected from the left hemisphere of each subject. BA 24 was taken as the ventral anterior cingulate gyrus around the genu of the corpus callosum while BA 46 was defined as the lateral surface of the frontal lobe including approximately the middle third of the middle frontal gyrus and the most rostral portion of the inferior frontal gyrus.

***In Situ* Radioligand Binding with Autoradiography**

20µm frozen sections were cut from BA 24 and BA 46 tissue with a cryostat and mounted on to gelatinised slides. [³H]AMPA and [³H]kainate binding were performed as previously described (Scarr et al., 2005). To measure [³H]AMPA binding, sections were pre-incubated in 50mM TRIS-HCl, 2.5mM CaCl₂, 0.1M KCSN (pH7.4) (buffer 1) for 30 min, rinsed in water and dried. [³H]AMPA binding was performed by incubating 3 sections/subject in 1µM [³H]AMPA (PerkinElmer, Waltham, MA, USA) in buffer 1. Non-specific binding was measured in 2 sections/subject by displacing 1µM [³H]AMPA with 100µM quisqualic acid (Sigma-Aldrich, St. Louis, MO, USA). The sections were incubated for 45 min at 4°C. Following radioligand binding the slides were washed thrice for 15 sec in cold buffer 1, rinsed, dried, and partially fixed overnight in paraformaldehyde buffer.

To measure [³H]kainate binding, sections were pre-incubated in 50mM Tris-acetate (pH7.4) (buffer 2) for 30 min at 4°C, rinsed and dried. 3 sections/subject were incubated in 40nM [³H]kainate (PerkinElmer, Waltham, MA, USA) in buffer 2. Non-specific binding was measured in 2 sections/subject by displacing 40nM [³H]kainic acid with 1mM L-glutamic acid HCl (Sigma-Aldrich, St. Louis, MO, USA). Sections were incubated for 1 hr at 4°C and then washed twice for 2 min in buffer 2, rinsed, dried and partially fixed overnight in paraformaldehyde vapour.

The fixed slides were apposed to BAS-TR2025 plates (Fujifilm, Tokyo, Japan) with autoradiographic [³H]microscales[™] (Amersham Biosciences, Little Chalfont, UK). [³H]AMPA and [³H]kainate labelled slides were apposed for 14 days and 10 days, respectively. The plates were scanned in a BAS 5000 high resolution phosphoimager (Fujifilm, Tokyo, Japan) and the resulting images analysed using AIS imaging software (Imaging Research, St. Catharines, ON, Canada). The distribution of the binding of each

radioligand in each region of the cortex was carefully assessed, both visually and by placing a transept across each cortex and obtaining a binding profile, to determine whether binding was restricted to distinct layers within the grey matter. Radioligand binding was measured as an integrated measurement of signal intensity within these layers. Signal intensities were calibrated against the microscales and expressed as the average amount of total bound radioligand/estimated tissue equivalent subtracted from the average non-specific binding for each subject.

Statistics

The data was first analysed by the D'Agostino & Pearson omnibus normality test to determine whether they followed a Gaussian distribution. For data with a Gaussian distribution outliers were identified using Grubbs test (Iglewicz and Hoaglin, 1993). Pearson product moment tests were used to identify relationships between the radioligand binding levels and age, PMI, CNS pH and duration of illness that may have biased our data. $R^2 > 0.70$ was taken as indicative of a strong relationship as this value has been shown to be appropriate for small sample sizes (Gliner et al., 2002). 2-way ANOVA was used to determine whether binding density varied with gender or the incidence of suicide. The impact of any confounding factor that strongly influenced radioligand binding density was further investigated by covariant analysis. 2-way ANOVA was used to analyse data with a Gaussian distribution. Post-test analysis was performed using Bonferroni's multiple comparison test. Where the distribution was non-Gaussian appropriate non-parametric tests were used. Statistical significance was accepted at $p < 0.05$. Analyses were conducted using Prism 5.01 (Graphpad Software, La Jolla, CA, USA) software.

Results

In both BA 24 and BA 46, [^3H]AMPA and [^3H]kainate binding were localised to two layers (1 and 2) of differing binding densities within the grey matter. Radioligand binding layer 1 encompassed cortical laminae I-III whilst layer 2 overlaid laminae IV-VI. These binding patterns are consistent with previous findings in the ACC, visual and entorhinal cortices (Palomero-Gallagher et al., 2009; Zilles et al., 2004).

All binding data sets followed a Gaussian distribution ($3.68 > K2 > 0.13$; $P > 0.05$). There was no evidence of a strong relationship between the levels of [^3H]AMPA or [^3H]kainate binding and age, CNS pH, PMI or duration of illness in any diagnostic group ([^3H]AMPA: $0.63 > R^2 > 0.01$, $0.96 > P > 0.01$; [^3H]kainate: $0.44 > R^2 > 0.00$, $0.89 > P > 0.04$). Binding levels were also unaffected by gender ([^3H]AMPA: $F = 1.64$; $df = 1, 112$; $P = 0.20$; [^3H]kainate: $F = 0.96$; $df = 1, 112$; $P = 0.33$) or incidence of suicide ([^3H]AMPA: $F = 0.89$; $df = 1, 112$; $P = 0.34$; [^3H]kainate: $F = 0.48$; $df = 1, 112$; $P = 0.49$)

Analysis of [^3H]AMPA binding in MDD, BPD compared to controls revealed a significant effect of diagnosis ($F = 9.01$; $df = 2, 119$; $P < 0.001$). Post-hoc analysis showed that this effect resulted from an increase in [^3H]AMPA binding to both layers of BA 24 from subjects with MDD (Layer 1 = 20.7% increase; $t = 2.93$, $p < 0.05$; Layer 2 = 27.7% increase; $t = 2.96$, $p < 0.05$) compared to controls. [^3H]AMPA binding was not different in BA 24 from subjects with BPD and there was no change in the binding of either radioligand in BA46 from subjects with BPD and MDD ($2.02 > t > 0.20$, $p > 0.05$) (Figure 1A).

There was a significant effect of diagnosis on the density of [^3H]kainate binding in the two cortical regions examined ($F = 5.31$; $df = 2, 119$; $P = 0.006$). However, post-hoc analysis did not show any significant differences in radioligand binding between diagnoses within BA 24 or BA 46 (BA 24, Layer 1: $1.71 > t > 0.37$, $P > 0.05$; Layer 2: $2.45 > t > 0.1$, $P > 0.05$; BA 46, Layer 1: $2.61 > t > 0.37$, $P > 0.05$; Layer2: $2.61 > t > 0.15$, $P > 0.05$) (Figure 1B).

There was significant variation in [^3H]AMPA ($F = 31.84$, $df = 3, 119$; $p < 0.001$) and [^3H]kainate ($F = 6.05$, $df = 3, 108$; $p = 0.001$) binding levels between regions and layers. However, there was no significant interaction between regional variation and diagnostic variation in radioligand binding densities ([^3H]AMPA: $F = 0.86$, $df = 6, 119$, $P = 0.53$; [^3H]kainate: $F = 0.27$, $df = 6, 119$, $P = 0.95$).

Discussion

This study has shown a 20.7%-27.7% increase in [^3H]AMPA binding in BA 24, but not BA 46, from subjects with MDD. Increased AMPAR in MDD appears to be highly regionally specific with previous studies failing to show any change in [^3H]AMPA binding in the

hippocampus or the entorhinal and perirhinal cortices (Beneyto et al., 2007). Supporting our observations in the DLPFC, AMPAR subunit mRNA is also reported to be unchanged in the DLPFC (O'Connor et al., 2007).

There were no differences in [³H]AMPA binding in subjects with BPD compared to controls. These data, plus data from the hippocampus showing unchanged [³H]AMPA binding levels in BPD (Scarr et al., 2003), suggest that widespread changes in AMPAR do not occur in the CNS from subjects with mood disorders. This argument is supported by the finding that levels of AMPAR subunit transcript mRNA was not changed in the DLPFC from subjects with mood disorders (O'Connor et al., 2007).

The MDD and BPD subjects used in this study had been treated with a milieu of antidepressants and mood stabilizers prior to death and there remains a possibility that our data may have been impacted by a drug effect. Both acute and chronic treatment of rats with paroxetine or desipramine does not alter AMPAR protein expression in the frontal cortex suggesting our data is unlikely to reflect an antidepressant drug effect (Martinez-Turrillas et al., 2002). What about mood stabilisers and antipsychotics?

Neuroimaging studies have shown that the ACC is involved in depressed mood (Bench et al., 1992). Therefore, the increase in [³H]AMPA binding seen in BA 24 may be associated with depressive symptoms in MDD. This is supported by animal studies that show treating mice with the AMPAR potentiator LY 392098 improves performance on the forced swim test and tail suspension test models of depression (Li et al., 2001; Li et al., 2003), whilst pretreating ketamine-treated rats with the AMPAR antagonist NBQX abolishes the improved performance on the learned helplessness test and forced swim test that results from ketamine treatment alone (Maeng et al., 2008). Knockout mice lacking the AMPA subunit Glu-R1 gene *Gria1* also display poor performance on the learned helplessness model of depression (Chourbaji et al., 2008). These studies suggest that increased AMPAR signalling may be associated with reduced depression. Elevated AMPAR expression in BA 24, suggested by our data, is likely to increase AMPAR mediated signalling. Therefore, increased AMPAR could be a compensatory response to the molecular changes that result in depression rather than a cause of the illness.

[³H]kainate binding density was not altered in MDD and BPD compared to control levels in either BA 24 or BA 46. These data add to previous reports that [³H]kainate binding is

unchanged in BA 9 of the dorsolateral prefrontal cortex (Dean et al., 2001) or the hippocampus (Scarr et al., 2003) from subjects with BPD. Contrasting our data, mRNA expression of the kainate receptor GRIK5 subunit is decreased in MDD and BPD the prefrontal cortex (BA 8, BA9, BA 10 and BA 46) (Knable et al., 2001). Thus, while kainate receptor protein expression appears to be unchanged in mood disorders, it is possible that the subunit ratio of the kainate receptor tetramer varies between mood disorders and healthy controls, potentially affecting the kainate signalling.

This study supports a role for the AMPAR in the pathophysiology of MDD and adds to other findings showing other components of the glutamatergic signalling system are altered in mood disorders (e.g. NMDAR (Feyissa et al., 2009), the metabotropic glutamate receptors (Feyissa et al.), the glutamate transporters (Choudary et al., 2005) and glutamate itself (Auer et al., 2000)). Thus, there a need to continue to increase understanding of how the glutamatergic synapse is affected by the pathophysiology of mood disorders as a foundation to further probing potential glutamatergic based drug targets as potential new treatment sites.

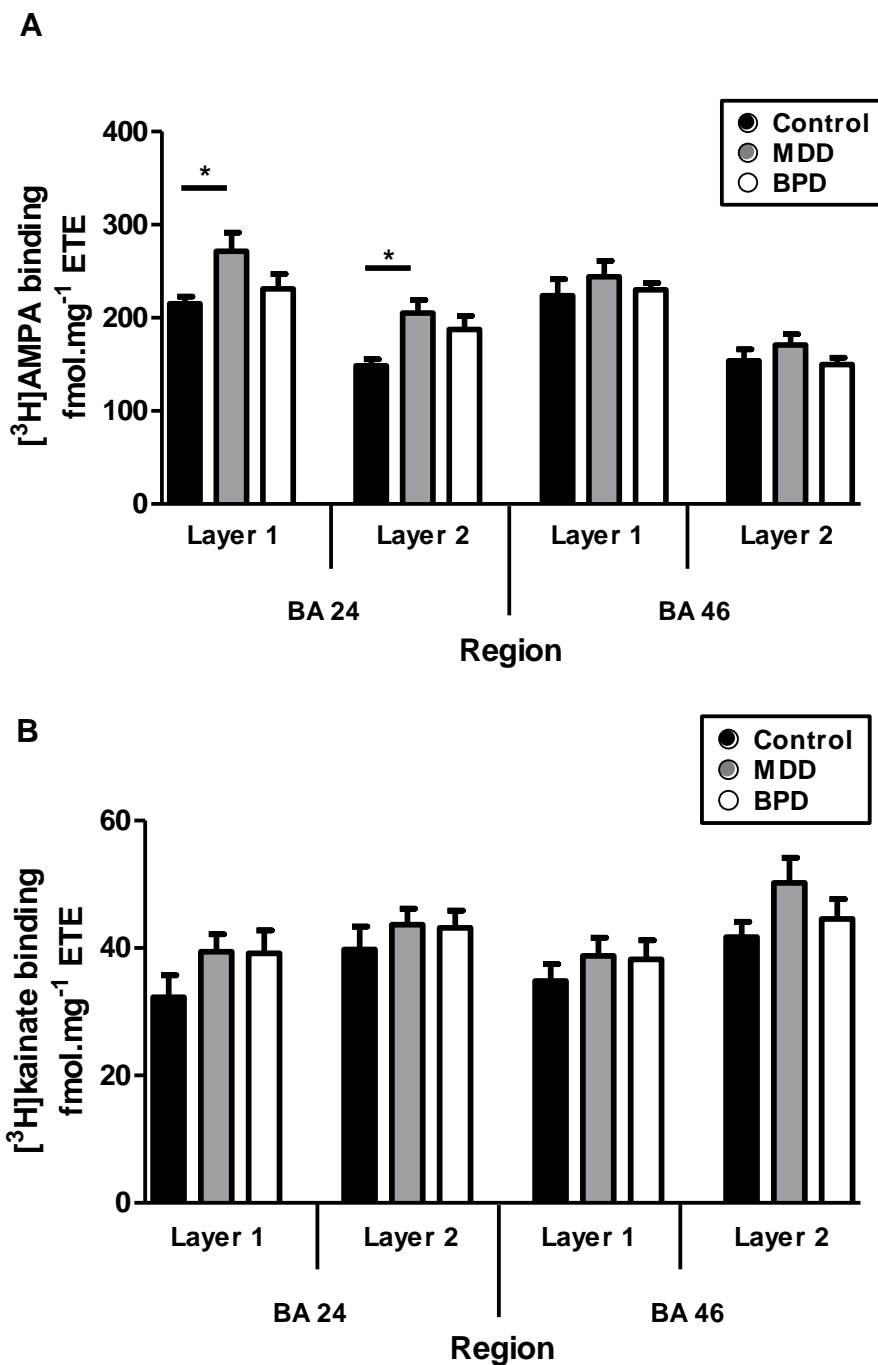
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Figure 1. The binding densities of (A) [³H]AMPA and (B) [³H]kainate in BA 24 and BA 46 from subjects with major depressive disorder (MDD) and bipolar disorder (BPD) compared to controls. Two discrete layers of radioligand binding were seen in both regions. Each layer was analysed separately. * = P<0.05 (Normally I like scatterplots but here they are a bit cloudy).



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