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AMPA receptor expression is increased post-mortem samples of the anterior cingulate from subjects with major depressive disorder

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Abstract

Background—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. While previous studies have suggested that the NMDA receptor may be involved in the pathophysiology of mood disorders, it is unclear whether the non-NMDA receptors are also involved. Therefore, we sought to examine whether the expression of the non-NMDA, ionotropic glutamate receptors, AMPA receptor and kainate receptor, is altered in mood disorders.

Methods—We used [^{3}H]AMPA and [^{3}H]kainate to measure the levels of AMPA and kainate receptor, respectively, in the anterior cingulate (BA 24) and dorsolateral prefrontal cortex (BA 46) from post-mortem CNS in 10 subjects with major depressive disorder, 10 subjects with bipolar disorder and 10 control subjects.

Results—A 20.7% to 27.7% increase in [^{3}H]AMPA binding density was seen in BA 24 ($p < 0.05$) but not BA 46 ($p > 0.05$) in major depressive disorder compared to control levels. [^{3}H]AMPA binding density was not changed in bipolar disorder in either BA 24 or BA 46 ($p > 0.05$) compared to controls. [^{3}H]Kainate binding was not changed in either BA 24 or BA 46 in either disorder compared to controls ($p > 0.05$).

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Conflict of Interest There were no conflicts of interest associated with this study.

Contributors Andrew Gibbons was involved in the design of the study statistical analysis of the data and oversaw the preparation of the manuscript. Lucy Brooks was involved in collecting the data and the statistical analysis of the data. Elizabeth Scarr was involved in the design of the study. Brian Dean was involved in the design of the study and heads the laboratory in which the study took place. All authors have made a significant contribution to the preparation of and have approved the manuscript.

Limitations—Small sample sizes (n = 10) were used in this study. The subjects were not drug naïve.

Conclusions—Our data suggests increased in AMPA receptor levels in the anterior cingulate are involved in the pathophysiology of major depressive disorder. This data has relevance for the development of new anti-depressant drugs targeted towards the AMPA receptors.

Keywords

AMPA Receptor; Kainate Receptor; Major Depressive Disorder; Bipolar Disorder Frontal Cortex

Introduction

Increased levels of glutamate, the major cortical excitatory neurotransmitter (McCormick, 1992; Tsumoto, 1990), in the blood of patients with major depressive disorder (MDD) suggest the glutamatergic system is involved in the pathophysiology of mood disorders (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). Furthermore, increased glutamate levels have been reported in the premotor cortex of post-mortem subjects with MDD and bipolar disorder (BPD) (Hashimoto et al., 2007), whilst brain imaging studies report reduced glutamate levels in the anterior cingulate of subjects with MDD during depressive episodes (Auer et al., 2000).

Several studies suggest a role for the N-methyl-D-aspartate receptor (NMDAR) in the pathophysiology of mood disorders (see Javitt, 2004; Petrie et al., 2000; Skolnick et al., 2009 for reviews). However, there appears to be little data on the possible involvement of the α-amino-3-hydroxy-5-methyl-4-isoxazoleprorionate receptor (AMPAR) and kainate receptor in the pathophysiology of mood disorders. This is a significant lack of knowledge given that 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, AMPAR potentiators have been shown to reduce immobility in rodent, behavioural despair models of depression (Li et al., 2001; Li et al., 2003). Notably, the kainate receptor is thought to regulate glutamate release (Jouhanneau et al., 2011). Thus, abnormal kainate receptor expression could have a considerable impact on glutamatergic neurotransmission. Post-mortem studies have reported decreased [^{3}H]kainate binding in the dorsolateral prefrontal cortex and hippocampus from subjects with schizophrenia (Kerwin et al., 1988; Scarr et al., 2005). Comparable data on [^{3}H]kainate binding in the cortex of subjects with mood disorders is not available. However, mRNA expression of the kainate receptor Glu-R5 subunit is decreased in the prefrontal cortex from subjects with MDD and BPD (Knable et al., 2001).

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) (Brodmanns Area [BA] 46) and the anterior cingulate (ACC) (BA 24), two regions high-lighted by neuroimaging studies as being affected in mood disorders (Soares and Mann, 1997).

Methods

Tissue collection

Post-mortem BA 24 and BA 46 tissue from 10 subjects with MDD, 10 subjects with BPD and 10 subjects with no history of psychiatric illness (controls) was obtained from the

Victorian Brain Bank Network following approval from the Ethics Committee of the Victorian Institute of Forensic Medicine and the Mental Health Research and Ethics Committee of Melbourne Health. MDD and BPD were diagnosed according to DSM-IV criteria (Hill et al., 1996; Roberts et al., 1998) following a case history review using the Diagnostic Instrument for Brain Studies (DIBS) (Keks et al., 1999). The age, gender, post-mortem interval (PMI), CNS pH and duration of illness (DOI) 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. Postmortem interval (PMI) was taken as the time between death and autopsy. 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).

In Situ Radioligand Binding with Autoradiography

All experiments were performed blind to diagnosis. 5× 20μm frozen sections were cut from BA 24 and BA 46 of each subject and mounted on to gelatinised slides. Single point saturation measurements were used to measure [^{3}H]AMPA and [^{3}H]kainate binding, as previously described (Scarr et al., 2003; Scarr et al., 2005), whereby radioligand binding was measured at a concentration of 3× the Kd of the radioligand for the receptor of interest, as determined in control cortical tissue, to ensure saturation of the receptor binding sites.

To measure [^{3}H]AMPA binding, sections were pre-incubated in 50mM TRIS-HCl, 2.5mM $CaCl_2$, 0.1M KCSN (pH7.4) (buffer 1) for 30 min, rinsed in water and dried. [^{3}H]AMPA binding was performed by incubating 3 sections/subject in 1μM [^{3}H]AMPA (PerkinElmer, Waltham, MA, USA) in buffer 1. Non-specific binding was measured in 2 sections/subject by displacing 1μM [^{3}H]AMPA with 100μM quisqualic acid (Sigma-Aldrich, St. Louis, MO, USA). The sections were incubated for 45 min at 4°C and washed thrice for 15 sec in cold buffer 1.

To measure [^{3}H]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 [^{3}H]kainate (PerkinElmer, Waltham, MA, USA) in buffer 2. Non-specific binding was measured in 2 sections/subject by displacing 40nM [^{3}H]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. Following the buffer washes, all section were rinsed in water, dried and partially fixed overnight in paraformaldehyde vapour.

The fixed slides were apposed to BAS-TR2025 plates (Fujifilm, Tokyo, Japan) with autoradiographic [^{3}H]microscales™ (Amersham Biosciences, Little Chalfont, UK) for 14 days ([^{3}H]AMPA) and 10 days ([^{3}H]kainate). The plates were scanned in a BAS5000 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 cortical region was carefully assessed, both visually and by measuring changes in the signal intensity along a transept of the cortex and generating a binding density profile across the grey matter, 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.

Following autoradiography, representative sections were fixed in 10% paraformaldehyde for 45 mins and stained with cresyl violet (0.1% cresyl violet acetate for 25 min and destained in dH_20) to localise the layers of binding within the grey matter to cortical laminae.

Statistics

The data was first analysed by the D'Agostino & Pearson omnibus normality test to determine whether they followed a Gaussian distribution. 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 followed by Bonferroni post-hoc analyses were used to analyse data with a Gaussian distribution. 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, [^{3}H]AMPA and [^{3}H]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 overlayed 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 [^{3}H]AMPA or [^{3}H]kainate binding and age, CNS pH, PMI or duration of illness in any diagnostic group ([^{3}H]AMPA: [upper and lower values across all parameters] $0.63 > R^2 > 0.01$, $0.96 > P > 0.01$; [^{3}H]kainate: $0.44 > R^2 > 0.00$, $0.89 > P > 0.04$). Binding levels were also unaffected by gender ([^{3}H]AMPA: $F = 1.64$; $df = 1, 112$; $P = 0.20$; [^{3}H]kainate: $F = 0.96$; $df = 1, 112$; $P = 0.33$) or incidence of suicide ([^{3}H]AMPA: $F = 0.89$; $df = 1, 112$; $P = 0.34$; [^{3}H]kainate: $F = 0.48$; $df = 1, 112$; $P = 0.49$)

Analysis of [^{3}H]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 [^{3}H]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. [^{3}H]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 [^{3}H]kainate binding in the two cortical regions examined ($F = 5.31$; $df = 2, 119$; $P = 0.006$). However, despite a trend towards increased binding in MDD and BPD in both regions, post-hoc analysis failed to resolve 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: $2.61 > t > 0.37$, $P > 0.05$; Layer 2: $2.61 > t > 0.15$, $P > 0.05$) (Figure 1B).

There was significant variation in [^{3}H]AMPA ($F = 31.84$, $df = 3, 119$; $p < 0.001$) and [^{3}H]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 ([^{3}H]AMPA: F = 0.86, df = 6, 119, P = 0.53; [^{3}H]kainate: F= 0.27, df= 6, 119, P= 0.95).

Discussion

This study has shown a 20.7%–27.7% increase in [^{3}H]AMPA binding in BA 24, but not BA 46, from subjects with MDD. Increased AMPAR in MDD appears to be regionally specific with previous studies failing to show any change in [^{3}H]AMPA binding in the hippocampus or the entorhinal and perirhinal cortices (Beneyto et al., 2007). There were no differences in [^{3}H]AMPA binding in subjects with BPD compared to controls. These data, plus data from the hippocampus showing unchanged [^{3}H]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 (see table 1) and there remains a possibility that our data may have been impacted by a drug effect. Both acute and chronic treatment of rats with the antidepressants paroxetine and desipramine does not alter AMPAR protein expression in either membrane fractions or total protein isolates from the frontal cortex (Martinez-Turrillas et al., 2002). However, fluoxetine has been shown to alter the phosphorylation state of the AMPAR subunits (Svenningsson et al., 2002) and this might affect the binding affinity of [^{3}H]AMPA for the AMPAR without affecting expression levels. While we expect our methodology, which measured [^{3}H]AMPA binding at 3× its Kd for the AMPAR, is sufficiently robust to be unaffected by changes in binding affinity, we cannot exclude the possibility that case medication history could have affected our binding data.

Neuroimaging studies have shown that the ACC is involved in depressed mood (Bench et al., 1992). Therefore, the increased [^{3}H]AMPA binding seen in BA 24 may be associated with depressive symptoms in MDD. This is supported by studies reporting that treating mice with the AMPAR potentiator LY392098 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 also display poor performance on the learned helplessness model of depression (Chourbaji et al., 2008), suggesting 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.

[^{3}H]kainate binding density was not altered in either BA 24 or BA 46 from subjects with MDD and BPD compared to controls. These data add to previous reports that [^{3}H]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. However, mRNA expression of the kainate receptor Glu-R5 subunit is decreased the prefrontal cortex from individuals with MDD and BPD (Knable et al., 2001). Thus, while kainate receptor protein expression appears to be unchanged in mood disorders, the subunit ratio of the kainate receptor tetramer may vary 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. 2010), the glutamate transporters (Choudary et al., 2005) and glutamate itself (Auer et al., 2000)). Thus, there is a need to continue to increase our 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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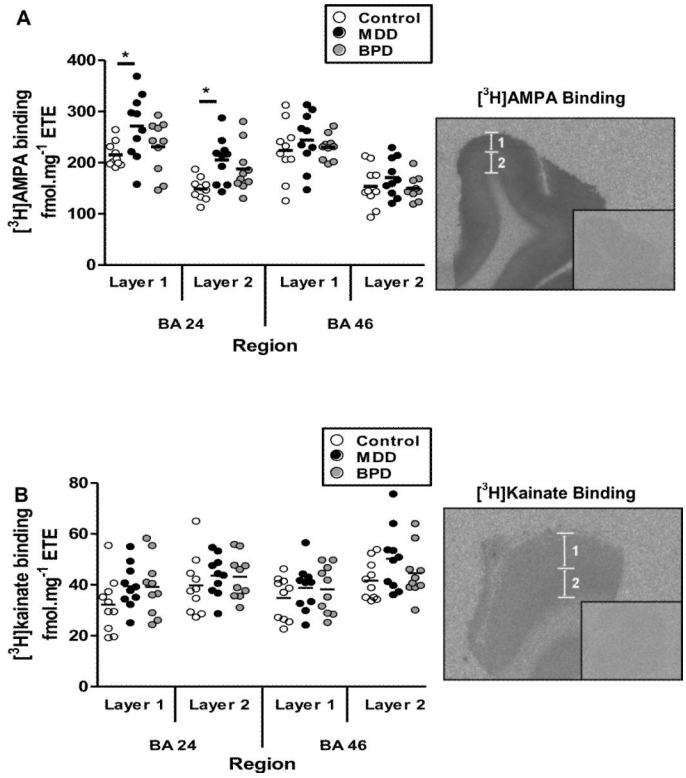

Figure 1.

The binding densities of (A) [^{3}H]AMPA and (B) [^{3}H]kainate in BA 24 and BA 46 from subjects with major depressive disorder (MDD) and bipolar disorder (BPD) compared to controls. Autoradiograms show the total and non-specific (inset) binding for both radioligands. Two discrete layers (layer 1 and layer 2) of radioligand binding were seen in both regions. Each layer was analysed separately. * = $P<0.05$.

Table 1

Demographic, CNS collection and toxicological data on subjects with MDD, BPD and age / sex matched controls used in this study. Drugs in brackets were prescribed within a month of death but not detected in the blood at autopsy.

Case	Diagnosis	Gender	Age	PMI	pH	DOI	Cause of death	Antidepressants	Dose (mg/L)	Mood stabilizers	Dose (mg/L)	Other	Dose (mg/L)
1	Control	Male	42	30.5	6.45		Ischemic heart disease						
2	Control	Male	52	33.75	6.52		Cardiomegaly; IHD/CAD						
3	Control	Female	47	24	5.89		Pulmonary embolus						
4	Control	Female	75	53	6.01		Multiple organ failure; Septicaemia						
5	Control	Male	70	59	6.11		RV Rupture following pericardial drainage						
6	Control	Male	75	69.4	6.19		Cardiogenic shock						
7	Control	Male	55	30.5	6.69		Coronary artery atherosclerosis						
8	Control	Male	66	71.75	6.47		Coronary artery atheroma						
9	Control	Female	80	55	6.28		Ischemic heart disease						
10	Control	Female	63	50.25	6.55		Coronary artery atherosclerosis						
11	MDD	Male	37	57.75	6.84	14	Hanging	Sertraline	0.2			Ethanol	Detected
12	MDD	Male	51	41	6.71	15	Hanging	Clomipramine Desmethyclomipramine	0.3 Detected				
13	MDD	Female	50	50.5	6.85	40	Mixed drug toxicity					Diazepmam Nordiazepam Codeine Paracetamol Propoxyphene Norpropoxyphene Metoclopramide Verapamil Zolpidem Tramadol	~0.8 ~1.5 0.1 ~220 7.4 27 ~53 ~3.5 ~0.1 ~15.2
14	MDD	Female	77	16.7	6.49	26	Doxepin toxicity		Doxepin	5.4			
15	MDD	Male	69	44.5	6.45	20	Drowning					Diphenhydramine	~4
16	MDD	Male	79	24	6.32	17	CO poisoning		Nortriptyline	~0.7		Nordiazepam Paracetamol	~0.1 ~1000
17	MDD	Male	55	47.75	6.60	3	Hanging		Venlafaxine	~0.2			
18	MDD	Male	68	60.75	6.65	9	Hanging		Citalopram Mianaserin	Trace ~0.1		Temazepam	~0.2
19	MDD	Female	87	24.5	6.44	7	Chest infection		(Setraline)				

Case	Diagnosis	Gender	Age	PMI	pH	DOI	Cause of death	Antidepressants	Dose (mg/L)	Mood stabilizers	Dose (mg/L)	Other	Dose (mg/L)
20	MDD	Female	51	23.5	6.49	25	Toxicity to Quetiapine		(Mirtazapine)			Diazepam Nordiazepam Quetiapine	100 ~0.4 ~0.3
21	BPD	Male	38	24	6.42	8	CO poisoning					Ethanol Codeine Paracetamol Doxylamine	Detected 0.3 46 0.2
22	BPD	Male	59	34	6.46	24	Ruptured aorta						
23	BPD	Female	42	25	6.54	20	Hanging	Venlafaxine	~0.5	(Lithium)		Ethanol Diazepam	Detected ~0.1
24	BPD	Female	64	26	6.46	8	IHD/CAD	(Venlafaxine)		(Na Valproate)			
25	BPD	Male	66	17	6.41	12	Aspirated on food						
26	BPD	Male	79	8.25	6.09	17	Cholecystitis in association with cardiomegaly			Na Valproate	16	Zolpidem	0.2mg
27	BPD	Male	59	37.5	5.97	8	Ischemic heart disease; Coronary artery atherosclerosis			(Lithium)			
28	BPD	Male	61	58	6.44	40	Acute myocardial infarction			(Na Valproate)			
29	BPD	Female	74	45	6.26	35	Combined drug toxicity	Amitriptyline Nortriptyline Dothiepin	4.9 3.1 4.0	Na Valproate	10		
30	BPD	Female	56	86	6.43	N/A	CO poisoning	Venlafaxine	~0.6	Carbamazepine	~1.8	Ethanol Paracetamol	Detected Trace

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