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Glucocorticoid and Mineralocorticoid Receptor Expression in the Human Hippocampus in Major Depressive Disorder

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Abstract

Approximately 50% of mood disorder patients exhibit hypercortisolism. Cortisol normally exerts its functions in the CNS via binding to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). Both MR and GR are highly expressed in human hippocampus and several studies have suggested that alterations in the levels of MR or GR within this region may contribute to the dysregulation in major depressive disorder (MDD). Studies have also shown functional heterogeneity across the hippocampus, with posterior hippocampus preferentially involved in cognitive processes and anterior hippocampus involved in stress, emotion and affect. We therefore hypothesize that GR and MR expression in hippocampus of control and MDD patients may vary not only with disease, but also with regional specificity along the anterior/posterior axis. Student's t-test analysis showed decreased expression of MR in the MDD group compared to controls in the anterior, but not the posterior hippocampus, with no significant changes in GR. Linear regression analysis showed a marked difference in MR:GR correlation between suicide and non-suicide patients in the posterior hippocampus. Our findings are consistent with previous reports of hippocampal corticosteroid receptor dysregulation in mood disorders, but extend those findings by analysis across the anterior/posterior axis of the hippocampus. A decrease in MR in the anterior but not posterior hippocampus of MDD patients emphasizes the important functional role of the anterior hippocampus in neuroendocrine regulation in humans.

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis controls the mammalian stress response by regulating hypothalamic CRH, pituitary ACTH, and adrenal glucocorticoid production and release. Dysregulation within this axis has been linked to major depressive disorder (MDD) and other mood and anxiety disorders. The HPA axis hyperactivity in MDD is often linked to increased CRH drive (Wang, Kamphuis et al. 2008) and/or impaired negative feedback by glucocorticoids in the HPA axis (Bardeleben and Holsboer 1989). In fact, increased glucocorticoid secretion and insensitivity to glucocorticoid feedback have been observed in approximately 50% of depression cases (Halbreich, Asnis et al. 1985; Akil, Haskett et al. 1993; Checkley 1996). The negative glucocorticoid feedback is critical for homeostasis, and

it occurs at multiple levels including anterior pituitary corticotrophs, the paraventricular nucleus of the hypothalamus, and the hippocampus.

The hippocampus is particularly sensitive to glucocorticoid levels, and normally exhibits a tonic negative regulation on HPA function (Herman, Cullinan et al. 1992; Herman, Cullinan et al. 1995). Glucocorticoids in the hippocampus also contribute to neuronal excitability and neuroplasticity, key aspects of cognitive function. The mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) mediate the actions of glucocorticoids. These receptors act as ligand-activated transcription factors, affecting the transcription of a wide variety of genes. Because MR has a 10 fold higher affinity for cortisol (or corticosterone) than GR (Reul and de Kloet 1985), MR becomes occupied at low cortisol concentrations such as those observed under basal physiological conditions (de Kloet, Rots et al. 1994). GR is activated only when circulating levels of cortisol increase, i.e during the peak of the circadian rhythm or under stressful conditions (De Kloet, Vreugdenhil et al. 1998). At the cellular level, MR and GR exert their action largely as dimers, with MR-MR homodimers, GR-GR homodimers, and MR-GR heterodimers present in cells that express both receptors (Trapp, Rupprecht et al. 1994). The coordinated activity of MR and GR allows complex regulation by glucocorticoids, where the corticosteroid-mediated profile of gene expression depends not only on the ligand concentration, but also on the MR and GR expression levels and the ratio of MR to GR in the cell.

Both MR and GR are highly expressed in human hippocampus (Seckl, Dickson et al. 1991; Lopez, Chalmers et al. 1998; Watzka, Beyenburg et al. 2000). Several studies have suggested that alterations in the levels of MR or GR within the hippocampus may contribute to the HPA axis dysregulation in MDD and other mood disorders. Webster et al (2002) has shown decreased GR mRNA in the hippocampus in depression exclusively in the dentate gyrus, while Alt et al (2010) found no significant differences in total hippocampal GR mRNA in controls and MDD subjects. In contrast, studies by Klok et al. (2011) and Lopez et al. (1998) demonstrate decreased expression of MR mRNA in human postmortem brains from MDD patients or suicide subjects with a previous history of MDD. Together, these studies suggest that alterations in hippocampal MR or GR expression and resultant MR/GR ratio may contribute to psychiatric illness.

While some of these studies analyzed total MR or GR mRNA expression in dissected human hippocampus, other studies used *in situ* hybridization to quantify mRNA differences within different subdivisions of the hippocampus. However, in addition to separate subdivisions in the hippocampal formation (DG, CA1, CA2, and CA3), the hippocampus also has different regions in both rodents (dorsal, ventral) and primate and humans (anterior and posterior), with separable inputs and targets (Moser and Moser 1998; Fanselow and Dong 2010). In the rodent, dorsal and ventral hippocampi have been proposed to mediate spatial learning and anxiety –related measures, respectively (Bannerman, Yee et al. 1999; Bannerman, Rawlins et al. 2004; Leonardo, Richardson-Jones et al. 2006). In primates and humans, the differential roles of anterior and posterior hippocampus are less clear, but there is evidence of functional segregation (Strange, Fletcher et al. 1999). Some have proposed that the primate and human posterior hippocampi (equivalent to dorsal in rodents) are most important for processing spatial information (Colombo, Fernandez et al. 1998; Moser and

Moser 1998). Other studies in humans suggest that the anterior hippocampus (equivalent to ventral) is important for processing functions such as arousal, emotion and reward (Viard, Doeller et al. 2011). The functional heterogeneity across the hippocampus suggests that assessments of hippocampal MR and GR expression in psychiatric illness should include careful analysis of the neuroanatomical location of hippocampal blocks and sections. In this study, we therefore determine the GR and MR mRNA levels in anterior and posterior hippocampus of control and MDD brains using mRNA *in situ* hybridization analyses. We also examine the correlation between expression levels of MR and GR, as altered ratios or loss of correlation may be predictive of neuropsychiatric disease.

Materials and methods

Postmortem human brains were obtained from the Brain Donor Program at the University of California, Irvine, from individuals with a clinical diagnosis of major depression disorder (MDD), bipolar disorder (BPD), and controls with no personal or familial history of psychiatric symptoms. All procedures were approved by the local ethics committee and performed under the parameters of the declaration of Helsinki.

Brains were selected using the University of California, Irvine Dept. of Psychiatry and Human Behavior Psychological Autopsy Protocol; the subjects' clinical records exhibit no clinical evidence of neurodegenerative disorders, such as Parkinson's, Huntington's, dementia, or impairment as a result of cerebrovascular accident (CVA). All subjects were screened to assure zero agonal factors on a scale from 0 to 4; brain pH was above 6.5 to insure maximum mRNA preservation (Li, Vawter et al. 2004; Vawter, Shannon Weickert et al. 2004). With the exception of one patient all subjects had a rapid death (within one hour of fatal event). For detailed subject data see Table 1.

Blocks from 27 subjects were processed as follows. Frozen tissue blocks were sectioned on a cryostat at 10µm, mounted onto Superfrost®/ Plus glass slides (Fisher Scientific, USA), and stored at -80 °C until needed. A detailed description of the *in situ* hybridization protocol can be found in the work of Kabbaj et al.(2000). In brief, sections were taken at 500µm intervals, post-fixed in 4% paraformaldehyde, washed in 2X SCC and incubated for 10 min in 0.1M TEA. Sections were subsequently rinsed in distilled water, dehydrated in ascending alcohol concentrations, air dried, and hybridized with ³⁵S-labeled cRNA probes. Human cRNA probes for MR (Genbank M16801, nucleotides 10-729) and GR (Genbank M69104, nucleotides 775-1330) were used. Labeled probes were diluted in hybridization buffer, applied to the sections, coverslipped and incubated overnight at 55°C. Slides were subsequently rinsed in 2X SSC, digested with ribonuclease (200µg/ml), washed in descending SSC concentrations to 0.1X SSC at 65 °C, dehydrated, and exposed to Kodak Biomax MR film (Eastman Kodak, Rochester, NY, USA). The exposure times were 3 weeks for MR and 6 weeks for GR.

Radiographic images of *in situ* hybridizations were scanned with a Microtek XL 1000 flat bed scanner with a transparency adapter. Using Silver Fast software the images were stored as 8 bit grayscale. Image resolution was set to 1600 pixels per inch at a 100% scale. Signal intensity of gene expression was quantified in a linear grayscale range and values generated

using Image J (National Institutes of Health, Bethesda, Maryland, USA) were expressed as optical density. Due to variability inherent to the dissection process we chose to disregard area as a component of the measurements.

A detailed anatomical analysis was performed on each slide to search for homologous regions of the hippocampus to ensure that all quantifications were performed at the same level. Quantification was performed on individual subfields (DG, CA1, CA2, CA3) and on the total hippocampus (all subfields combined). Due to the low levels of expression of GR on the CA1 region, we decided that the whole hippocampus quantification would be the more reliable data for statistical analysis, although it should be noted that the results are mainly driven by the values of the dentate gyrus.

Data from 2 to 4 sections per area per subject were averaged resulting in a mean optical density value for each subject. The areas representing the anterior and posterior hippocampus were selected according to the Atlas of the Human Brain (Mai et al 2008). The area considered as anterior hippocampus was equivalent to plates 31 to 34 of the atlas (about 12 to 16 mm caudal to the anterior white commissure), whereas the posterior hippocampus was homologous to plates 40 to 45 (about 23.9 to 30.5 mm caudal to the anterior white commissure).

All groups were analyzed by using a student's *t*-test, comparing each disease group against the control group, and linear regression to evaluate the relationship between MR and GR for each group.

Results

The results of the anatomical alignment indicated that 8 control and 10 MDD samples contained only the posterior hippocampus whereas 1 control and 3 MDD samples corresponded to the anterior hippocampus. Three control and 2 MDD samples contained both anterior and posterior areas. Measurements of the expression levels of MR and GR in the anterior and posterior hippocampus of control subjects that contained both levels indicated that the regional differences were substantial (Table 2); this difference coupled with the functional heterogeneity of these regions suggested that they should be evaluated separately. Figure 1 illustrates the morphological differences of MR and GR mRNA expression in anterior and posterior hippocampus levels in controls containing both areas as determined by in situ hybridization autoradiograms.

The distribution of MR and GR mRNA in subfields of the human hippocampus was similar to that described by Lopez et al (1998) and Seckl et al (1991). MR was found in all hippocampal subfields including the dentate gyrus, CA1, CA2 and CA3 and the subiculum, with the strongest expression observed in the dentate gyrus and CA3. GR was present mainly in the dentate gyrus and CA3, with low levels of expression in all other fields. MR expression levels were greater in the posterior compared to the anterior hippocampal regions, suggesting that the differential regional expression should be taken in to consideration for quantification purposes (see table2).

Posterior hippocampus

In the posterior hippocampus the results of student's *t*-test showed no significant differences in the total expression of MR or GR in MDD when compared to controls (Figure 2 A,B).

When the MDD group was divided by cause of death (suicide vs non-suicide), no significant differences were observed (Figure 2 C,D,E,F).

Linear regression analysis showed a positive correlation between the MR and GR expression in control subjects ($r^2=0.6415$, $p=0.0054$, $n=10$) (figure 3A). The MDD group as a whole also showed a positive, but slightly diminished MR-GR correlation ($r^2=0.5046$, $p=0.0096$, $n=13$) (Figure 3B). When examined according to the cause of death, the suicides showed a strong correlation ($r^2=0.9420$, $p=0.001$, $n=6$) (Figure 3C), but no correlation was observed in the non-suicide group ($r^2=0.1059$, $p=0.53$, $n=6$) (Figure 3D). There is a clear difference between suicide and non-suicide cases that was confirmed using Fisher's R to Z transformation ($p=0.02$). Suicide cases appear to have a stronger correlation when compared to controls, and a trend was observed in Fisher's analysis, but more subjects would be required to increase the power of this result.

Anterior hippocampus

Student's *t*-test analysis in the anterior hippocampus showed decreased expression of MR in the MDD group compared to controls ($p=0.03$, Figure 4 A). GR levels were similar in both groups (figure 4B). Due to the lower number of subjects available for this region on each group, correlation analysis was not performed.

Discussion

Our data have demonstrated marked differences in expression of MR mRNA along the anteroposterior axis in human hippocampus and a significant decrease in expression of MR mRNA in anterior, but not posterior, hippocampus of MDD subjects compared with controls. In contrast, no significant differences in GR mRNA expression were observed in the anterior or posterior hippocampus between controls and MDD patients. Our data therefore demonstrate a decreased MR/GR ratio in anterior, but not posterior, hippocampus in MDD patients vs controls, consistent with hypotheses of reduced functionality of MR, but normal GR, in depression (Gesing, Bilang-Bleuel et al. 2001; Young, Lopez et al. 2003). The study by Klok et al (2011) also found decreased MR mRNA in MDD patients, but used dissected hippocampal tissue that did not distinguish between the anterior and posterior regions of hippocampus. Similarly, Webster et al (2002) examined GR mRNA levels at mid-hippocampus, but no previous studies have examined GR mRNA in both anterior and posterior hippocampus of MDD patients and controls. Thus, our studies support the hypothesis of decreased hippocampal MR/GR ratio in depression, and also demonstrate the importance of quantitation of MR and GR levels not only across hippocampal subfields, but also across the anteroposterior axis.

The hippocampus is critical for learning and memory, but has also been shown to be a regulator of stress, emotion and affect. The functional differences along the dorsoventral axes of the rodent hippocampus have been recently reviewed (Fanselow and Dong 2010),

but the differences across the anteroposterior axis in primates and humans are less well characterized. Fanselow and Dong (2010) propose a clear separation between a dorsal (posterior in humans) zone that largely serves the cognitive function and a ventral (anterior in humans) zone that could be called the “affective” hippocampus. Differences in both connectivity and gene expression profiles between these zones support these functional differences (Thompson, Pathak et al. 2008; Dong, Swanson et al. 2009). The dorsal zone receives projections arising from the lateral and caudomedial portion of the entorhinal cortex, providing processed visio-spatial information (Dolorfo and Amaral 1998). In contrast, the ventral zone of the hippocampus, which has been associated with emotional behavior, has strong projections to prefrontal cortex, amygdala, and bed nucleus of the stria terminalis (Pitkanen, Pikkariainen et al. 2000) (Swanson and Cowan 1977; Sahay and Hen 2007), and to regions linked to HPA stress response and anxiety (Cullinan, Herman et al. 1993). Finally, chronic stress in rodents has been shown to decrease cell proliferation in ventral, but not dorsal hippocampus, and antidepressants appear to increase neurogenesis more robustly in ventral hippocampus compared to dorsal (Banasr, Soumier et al. 2006; Jayatissa, Bisgaard et al. 2006). If the hippocampal formation of humans shares the connectivity patterns and functional heterogeneity observed in animal models, the anterior hippocampus would be more tightly linked to neuroendocrine regulation and dysregulation, consistent with the observed decreased expression of MR mRNA in the anterior hippocampus in MDD subjects.

While no changes in MR or GR levels were observed in posterior hippocampus of MDD patients vs controls in our studies, the number of subjects in this group allowed us to perform GR:MR correlation analysis. In both controls and MDD patients, a fairly strong positive correlation between GR:MR levels was observed in posterior hippocampus. However, when the MDD patients were separated by suicide vs non-suicide, the correlation was dramatically reduced in the non-suicide patients, while suicide patients maintained this correlation. In contrast, Lopez et al.(1998) has reported a loss of GR:MR correlation in suicide subjects. The reasons for the differences are not yet clear, but gender differences may be involved, as all the subjects in our study were male, while the subjects in the Lopez study included both sexes and mainly females. A similar observation was recently published by Wang et al. (2012), who reported a decrease of GR expression in depressed females compared to depressed males. This gender effect in the MDD group has also been observed in our studies (unpublished data).

In conclusion, we have shown that MR mRNA levels change across the anteroposterior axis in human hippocampus and that MR levels are decreased in anterior hippocampus in MDD subjects compared to controls. These findings are consistent with previous reports of hippocampal MR:GR dysregulation in depression or other mood disorders, but extend this work to distinct neuroanatomical regions within the hippocampus. The functional ties of ventral or anterior hippocampus to emotion, affect, stress and anxiety are consistent with our finding of reduced MR mRNA levels in MDD patients in the anterior hippocampus. Finally, our results suggest that normal HPA axis responsiveness may be dependent on a fine control exerted by hippocampal MR and GR, not only through the total amounts of receptors but also throughout the relative abundance of each receptor type in specific hippocampal regions. Hence, alterations in either the total amount or the balance between the two

corticosteroid receptors in key hippocampal regions may contribute to stress system dysregulation in MDD and to other mood and anxiety disorders as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Corticosteroid receptor expression in the human hippocampus. Upper row: MR expression in the anterior (A) and posterior (B) hippocampus including all subfields in a control subject. Lower row: GR expression in the anterior (C) and posterior (D) hippocampus including all subfields in the same control subject.

Figure 2.

Corticosteroid receptor expression levels in the posterior hippocampus. No differences are observed between control and MDD subjects in MR (A) or GR (B) levels. Also, no differences are observed between control and MDD suicides or non-suicides in MR (C,E) or GR (D,F) levels.

Figure 3.

Linear regression analysis showed a similar correlation between MR and GR in MDD compared to controls (A,B). When subjects were divided by cause of death (C,D), a clear difference appeared between MDD suicides, which show a strong correlation and MDD non-suicides, where the correlation was lost.

Figure 4.

Corticosteroid receptor expression in the anterior hippocampus. A. In situ hybridization results revealed a significant decrease in MR expression in anterior hippocampus in MDD patients compared to controls ($p=0.03$). B. No significant change in GR expression in anterior hippocampus was observed in control and MDD patients.

Table 1

The table shows the serial numbers, general demographics, cause of death, pH, agonal factor scores (AFS) and post mortem intervals (PMI) for the subjects used in the study. SMC: sudden medical condition. LTMC: long-term medical condition. Acc/overdose: accidental overdose. C: Caucasian. AA: African American.

	Subject ID	Dx	Region	Gender	Age	Cause of Death	AFS	pH	PMI	Race
1	2315	MDD	Ant	M	58	Suicide	0	6.9	24	C
2	3481	MDD	Ant	M	66	SMC	0	7.05	32	C
3	3064	MDD	Ant	M	46	SMC	0	6.9	27	C
4	2944A	MDD	Ant/post	M	52	SMC	0	6.8	16	C
5	2267	MDD	Ant/post	M	19	Suicide	0	7.1	18	C
6	3204B	MDD	Post	M	46	SMC	0	6.5	24	C
7	3426	MDD	Post	M	63	SMC	0	7.1	29	C
8	4282B	MDD	Post	M	51	SMC	0	6.5	29	C
9	4590B	MDD	Post	M	55	Suicide	0	6.9	25	C
10	4626B	MDD	Post	M	64	Suicide	0	7.0	12	C
11	3168	MDD	Post	M	39	Suicide	0	6.7	28	C
12	4188A	MDD	Post	M	65	Suicide	0	6.8	27	C
13	4232	MDD	Post	M	54	Suicide	0	6.7	25	C
14	3071	MDD	Post	M	49	Acc/overdose	0	7.0	31	C
15	3169C	MDD	Post	M	35	Acc/overdose	0	7.0	25	C
16	3519	Control	Ant	M	65	SMC	0	6.8	14	AA
17	3572	Control	Ant/post	M	49	SMC	0	6.6	28	C
18	2292	Control	Ant/post	M	55	SMC	0	6.89	15	C
19	2805	Control	Ant/post	M	45	SMC	0	6.86	21	C
20	1834	Control	Post	M	40	LTMC	0	6.7	12	C
21	2619	Control	Post	M	48	SMC	0	6.7	20	C
22	3520	Control	Post	M	74	SMC	0	7.2	19	C
23	3993	Control	Post	M	73	SMC	0	6.7	27	C
24	4235A	Control	Post	M	42	SMC	0	7.0	20	C
25	4327	Control	Post	M	56	SMC	0	6.6	9	C
26	4387A	Control	Post	M	53	SMC	0	6.6	14	C

Subject ID	Dx	Region	Gender	Age	Cause of Death	AFS	pH	PMI	Race	
27	4638	Control	Post	M	78	SMC	0	6.7	22	C
Averages					53.2	0	6.8			

Table 2

The table shows the psychiatric medication status of the MDD group used in this study. Since there is no consistency among subjects we removed medication as a variable of the study.

	Subject ID	Dx	Region	Medication status
1	2315	MDD	Ant	Prozac, Ativan
2	3481	MDD	Ant	Zoloft
3	3064	MDD	Ant	Paroxetine
4	2944A	MDD	Ant/post	Prozac, Wellbutrin
5	2267	MDD	Ant/post	None
6	3204B	MDD	Post	None
7	3426	MDD	Post	None
8	4282B	MDD	Post	Prozac, Wellbutrin
9	4590B	MDD	Post	Ativan
10	4626B	MDD	Post	Ativan
11	3168	MDD	Post	Paroxetine
12	4188A	MDD	Post	None
13	4232	MDD	Post	Ambien
14	3071	MDD	Post	Ambien, Zoloft, Buspar, Xanax
15	3169C	MDD	Post	Xanax, Prozac, Zoloft, Wellbutrin

Table 3

Comparison of mean values for MR and GR expression in the anterior and posterior hippocampus of control subjects. MR values in the anterior and posterior hippocampus are significantly different, suggesting that the analysis should be separated by regions.

Hippocampus Region	MR	GR
Anterior	0.24 ± 0.04	0.63 ± 0.08
Posterior	0.48 ± 0.04	0.67 ± 0.06