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Research report

Unaltered histaminergic system in depression: A postmortem study

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ABSTRACT

Background: Rodent experiments suggested that the neuronal histaminergic system may be involved in symptoms of depression.

Methods: We determined, therefore, in postmortem tissue of 12 mood disorder patients (8 major depression disorder (MDD) and 4 bipolar disorder (BD)) and 12 well matched controls the expression of the rate-limiting enzyme for histamine production and histidine decarboxylase in the tuberomamillary nucleus (TMN) by quantitative in situ hybridization. In addition we used qPCR to determine the expression of the 4 histamine receptors and of the enzyme breaking down histamine, histamine N-methyltransferase (HMT), in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulated cortex (ACC).

Results: No changes were observed in the expression of these molecules, except for a significant lower HMT mRNA expression in the ACC of MDD subjects.

Limitations: Several inherent and potentially confounding factors of a postmortem study, such as medication and cause of death, did not seem to affect the conclusions. The group size was relatively small but well documented, both clinically and neuropathologically.

Conclusion: Except for a lower HMT mRNA expression in the ACC of MDD subjects, the neuronal histaminergic system did not show significant changes, either in the rate limiting enzyme involved in its production or in its receptors in 2 main projection sites, the ACC/DLPFC.

1. Introduction

The neuronal histaminergic system was proposed to be involved in symptoms of depression, such as disturbances in attention, appetite and sleep (Haas et al., 2008). Rodent studies have shown that histamine activates the major stress systems in the hypothalamus that are also involved in the pathogenesis of depression (Ito, 2000). Therefore, the present study investigates whether this system shows alterations in depression, a disorder that is characterized by hyperactive stress systems (Bao et al., 2005).

2. Methods

2.1. Postmortem brain material

Postmortem brain tissues of patients with major depressive disorder (MDD) or bipolar disorder (BD) and of well matched controls were obtained through the Netherlands Brain Bank (NBB) following permission from patients or their next of kin for a brain autopsy and for the use of brain material and clinical data for research purposes. DSM-IV criteria were used for the diagnosis of MDD or BD during life. The criteria for the presence, duration and severity of symptoms of either MDD or BD, as well as the exclusion of other psychiatric and neurological disorders, were systematically scored by a qualified psychiatrist (Drs. W.J.G. Hoogendijk, E. Vermette or G. Meynen). For detailed clinicopathological information on patients and matched controls (see Table 1). Systematic neuropathological analyses were performed on all brains as described before (van de Nes et al., 1998).

2.2. HDC-mRNA in situ hybridization in the TMN

Changes in the neuronal histamine production were studied in formalin-fixed paraffin-embedded hypothalamic tissue by means of in situ hybridization. The expression of the rate limiting enzyme for histamine production, histidine decarboxylase (HDC), in the hypothalamic tuberomamillary nucleus (TMN) was determined in 12 mood disorder subjects (8 MDD and 4 BD). From 11 mood disorder patients, the total number of neurons expressing corticotropin-releasing hormone (CRH) positive neurons in the paraventricular nucleus (PVN) was available from previous work by our group (Bao et al., 2005).

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Table 1
Clinico-pathological information of patients with mood disorders and control subjects.

	NBB number		Sex	Age at death (yr)	Age at onset (yr)	CTD (h)	MTD	PMD (min)	Fix (d)	CSF pH	Brain weight (g)	Used for	RIN value (DLPFC)	RIN valve (ACC)	Cause of death
Patients	99–118	BD	M	68	32	23:15	10	355	33	6.82	1204	TMN, DLPFC	7.7	–	Cardiac ischemia
	00–111	BD	M	70	35	2:45	10	290	43	6.26	1490	TMN, DLPFC	8.10	–	Cardiac arrest
	00–088	BD	M	73	28	9:30	1	315	36	6.38	1260	TMN, ACC, DLPFC	7.2	7.5	Dehydration
	02–014	BD	M	68	66	2:45	2	1106	–	6.64	1424	ACC, DLPFC	8.1	7.2	Subdural hematoma after a fall
	06–075	BD	F	80	45	9:30	10	570	37	6.33	1190	ACC, DLPFC	6.3	6.3	Acute heart death
	00–074	BD	M	78	68	23:00	6	455	47	6.27	1227	ACC, DLPFC	7.3	6.7	Metastatized colon carcinoma
	07–076	BD	F	79	31	3:10	11	445	–	6.25	1231	DLPFC	7.2		Sudden death
	06–021	BD	M	70	64	13:07	3	383	44	6.5	1488	ACC, DLPFC	7.1	7.0	Pneumonia and sever neck trauma
	07–060	BD	M	93	78	21:10	9	360	45	6.37	1459	ACC	–	7.7	Sudden death
	97–058	BD	F	90	35	10:15	5	390	33	N.D.	1143	ACC, DLPFC	7.4	7.1	Pulmonary embolism
	92–003	MD	F	55	40	7:45	11	294	52		1320	TMN	–	–	Heart failure
	94–112	MD	M	61	50	4:40	10	2420	42		1424	TMN	–	–	Pneumonia
	94–032	MD	M	71	53	16:15	2	975	38		975	TMN	–	–	Pneumonia, cerebral ischemia,
	94–055	MD	F	72	53	4:20	4	1705	35		1116	TMN	–	–	Heart failure, septic shock, pyelonephritis
	94–017	MD	F	72	54	19:00	1	1320	39		1287	TMN	–	–	Pneumonia
	95–036	MD	M	74	74	17:05	3	3775	35		1444	TMN	–	–	Strangulation (suicide)
	93–115	MD	M	79		17:50	9	1270	28		1530	TMN	–	–	Jump off from floor (suicide)
	02–051	MD	M	81	48	15:30	6	360	34	6.50	1345	TMN, ACC, DLPFC	7.3	8.0	Renal insufficiency
	01–074	MD	M	45	32	2:30	6	420	54	6.55	1427	ACC, DLPFC	8.00	7.0	Brainstem hemorrhage
	06–011	MD	F	60	54	16:10	1	260	34	N.D.	1080	ACC, DLPFC	8.90	8.0	Legal euthanasia because of metastasized mammary carcinoma
	06–026	MD	M	70	47	8:00	3	435	40	6.55	1415	ACC, DLPFC	8.40	7.9	Respiratory insufficiency
	07–033	MD	M	88	69	21:15	5	397	34	6.26	1225	ACC, DLPFC	7.30	7.0	Multiple epileptic seizures
Median (TMN)			72	49	15:30	6	975	36	6.44	1320			–	–	
Median (DLPFC)			72	46	9:52	6	394	37	6.44	1246			7.3	–	
Median (ACC)			76	51	11:41	5	394	37	6.44	1303				7.15	
SEM (TMN)			2	4	2:05	1	334	2		50			–	–	
SEM (DLPFC)			3	4	2:00	1	55	2	0.05	36			0.18	–	
SEM (ACC)			4	5	1:59	1	63	2	–	39			–	0.16	
Controls	92–046	C-1	F	54	–	N.D.	4	780	31	–	1080	TMN	–	–	Traffic accident
	92–042	C-2	M	61	–	21:00	4	830	52	–	2220	TMN	–	–	Sudden death
	99–033	C-3	F	61	–	23:15	7	1065	44	–	902	TMN	–	–	Acute heart failure
	98–122	C-4	M	66	–	0:00	6	2460	49	–	1461	TMN	–	–	Spetic shock
	99–101	C-5	M	69	–	3:30	8	1155	41	–	1337	TMN	–	–	Pneumonia
	92–049	C-6	M	71	–	N.D.	4	340	32	–	1250	TMN	–	–	Sudden death
	06–028	C-7	M	76	–	20:00	4	1175	27	–	1514	TMN	–	–	Acute cardiac arrest
	97–156	C-8	F	77	–	8:30	11	160	47	–	1235	TMN	–	–	Septic shock
	94–039	C-9	M	78	–	12:00	1	3180	88	6.89	1354	TMN	–	–	Cardiac infarction
	99–116	C-10	M	78	–	16:15	9	260	43	6.98	1310	TMN	–	–	Pancreatic cancer
	93–059	C-11	M	78	–	12:10	1	362	70	7.03	1340	TMN	–	–	Cardio pulmonary insufficiency
	98–055	C-12	M	85	–	12:10	4	1280	31	6.31	1290	TMN	–	–	Cardiac infarction
	99–111	C-13	F	88	–	3:05	9	340	–	6.67	1054	DLPFC	6.9	–	Respiration insufficiency
	05–034	C-14	M	56	–	0:01	5	840	–	7.03	1323	DLPFC	8.5	–	Terminal congestive heart failure
	06–037	C-15	M	66	–	17:45	5	465	–	6.7	1590	DLPFC	7.8	–	Ruptured abdominal aorta aneurysm
	01–033	C-16	M	75	–	6:10	3	380	–	6.18	1180	DLPFC	7.3	–	Dehydration, adenocarcinoma, pneumonia
	97–156	C-17	F	77	–	8:30	11	160	–	6.37	1235	DLPFC	8.2	–	Septic shock
	00–067	C-18	M	73	–	0:01	6	1485	–	–	1267	DLPFC	7.8	–	Pulmonary embolism
	01–086	C-19	M	88	–	3:00	7	420	–	6.84	1398	DLPFC	8.1	–	Heart failure
	96–052	C-20	M	73	–	11:30	5	550	–	–	1500	DLPFC	8.5	–	Cardiac arrest due to tamponade
	97–039	C-21	M	87	–	15:00	4	240	–	6.94	1506	DLPFC	8.3	–	Cardial infarction
	98–006	C-22	M	50	–	11:00	1	510	–	6.65	1436	DLPFC	7.5	–	Cardiac arrest, sepsis
	05–044	C-23	M	80	–	0:01	6	435	34	5.8	1376	ACC, DLPFC	5.7	5.2	Cachexia and dehydration

05–068	C-24	M	56	–	4:45	10	555	32	6.54	1553	ACC	–	7.9	Cardial infarction
05–019	C-25	M	74	–	2:00	4	300	38	6.7	1125	ACC, DLPFC	8.3	8.1	Bronchocarcinoma
04–049	C-26	F	77	–	7:55	7	500	42	6.48	1312	ACC, DLPFC	6.1	5.9	Cachexia and uremia
04–057	C-27	F	81	–	13:10	8	400	33	7.16	1164	ACC, DLPFC	8.2	7.5	Legal euthanasia because of metastasized cholangiocarcinoma
05–017	C-28	M	87	–	4:00	3	620	33	6.32	1356	ACC	–	7.5	Pneumonia, heart infarction, renal insufficiency
06–080	C-29	F	89	–	21:30	12	385	30	6.46	1210	ACC	–	7.1	Ruptured abdominal aorta aneurysm
97–143	C-30	M	79	–	6:10	10	360	45	6.51	1392	ACC	–	8.6	Metastasized adeno- and lung carcinoma
97–043	C-31	M	68	–	9:05	4	610	38	7.08	1547	ACC	–	8.5	Cardiac infarction
95–062	C-32	M	80	–	14:30	6	270	52	6.22	1400	ACC	–	5.4	Renal insufficiency
05–073	C-33	M	87	–	8:05	10	365	33	6.96	1568	ACC	–	7.8	Unknown
04–020	C-34	M	96	–	13:27	2	323	31	6.7	1204	ACC	–	7.4	Pneumonia caused by aspiration
Median (TMN)			68	–	14:15	5	948	43	–	1294		–	–	
Median (DLPFC)			78	–	12:00	5	380	–		1310		7.80	–	
Median (ACC)			80	–	8:05	6	420	–	6.65	1392		–	7.50	
SEM (TMN)			3	–	4:04	1	247	3	–	394		–	–	
SEM (DLPFC)			3	–	1:57	1	318	–	0.11	48		0.29	–	
SEM (ACC)			3	–	1:26	1	68	–	0.09	34		0.34	0	
Level of significance (TMN)			0.795[a]	–	0.495[b]	0.632[b]	0.954[a]	0.204[a]	–	0.862[a]		–	–	
Level of significance (DLPFC)			0.581[a]	–	0.806[b]	0.565[b]	0.646[a]	–	0.073[a]	0.646[a]		0.259[a]	–	
Level of significance (ACC)			0.418[a]	–	0.266[b]	0.818[b]	0.931[a]	–	0.262[a]	0.686[a]		–	0.582[a]	

Abbreviations: ACC, anterior cingulated cortex; BD, bipolar depression; CTD, clock time at death; CSF, cerebrospinal fluid; d, days; DLPFC, dorsolateral prefrontal cortex; Fix, fixation time; MD, major depressive disorder; MTD, month of death; min, minutes; ND, not determined; PMD, post mortem delay; RIN, RNA integrity number; SD, standard deviation; TMN, tuberomamillary nucleus; yr, years; h, hours.

[a] Mann–Whitney-U-test.

[b] Mardia–Watson-test.

2.3. Quantitative PCR (qPCR) study in the frozen PFC

In addition, the mRNA expression of the four histamine receptors $H_{1-4}R$ and of the enzyme that breaks down histamine, histamine N-methyltransferase (HMT), was determined by qPCR in snap frozen tissue of the prefrontal cortex (PFC), which is a major site of termination of the histaminergic system. Primer sequences were described previously (van Wamelen et al., 2011). qPCR was performed in the dorsolateral PFC (DLPFC) in 14 mood disorder patients (5 MDD and 9 BD) and 14 matched controls, and in the anterior cingulated cortex (ACC) of 12 mood disorder patients (5 MDD and 7 BD) and 12 controls. Primer sequences for the reference genes *glyceraldehyde*-3-*phosphate dehydrogenase*, *actin*-β, *hydroxymethylbilane synthase*, *hypoxanthine phosphoribosyltransferase* 1, *ubiquitin C*, *tubulin*-α, *and tubulin*-β4 have been described before (Wang et al., 2008).

Detailed procedures of in situ hybridization and qPCR were published in our previous study (Liu et al., 2010; Shan et al., 2012).

2.4. Statistical analyses

The differences between the groups were statistically evaluated by the Mann–Whitney U test and correlation was tested with the Spearman test. $P<0.05$ level (two-tailed) was considered to be statistically significant.

3. Results

3.1. TMN

The HDC-mRNA levels in the TMN showed no significant differences between the mood disorder patients and the matched controls ($P=0.453$), or between MDD and matched controls ($P=0.529$), or between BD and matched controls ($P=0.773$). No correlation was found between HDC-mRNA and the number of CRH-expressing neurons in the mood disorders group ($P=0.190$, $n=11$). Because of the relatively limited number of subjects, correlations in the subgroups of BD, MDD and in their matched controls were not performed.

3.2. DLPFC and ACC

The mRNA expression levels of the $H_{1-4}R$ and of HMT of mood disorder patients and matched controls did not differ significantly either in DLPFC or ACC ($P\geq 0.117$). Unaltered histaminergic gene expressions in ACC or DLPFC were also observed in both MDD and BD with their matched controls ($P\geq 0.172$), except for a just significant lower HMT mRNA expression in the ACC of MDD and their matched controls ($P=0.047$).

4. Discussion

In general, except for a lower HMT mRNA expression in the ACC of MDD subjects, the neuronal histaminergic system did not show significant changes, in the rate limiting enzyme involved in its production and in its receptors in 2 main projection sites, the ACC/DLPFC.

The absence of a difference in the HDC experiment in depression and the lack of correlation between HDC-mRNA and the number of CRH-expressing neurons indicates that changes in the histaminergic system do not play a key role in the pathogenesis of depression. It should be noted that a higher histamine level was found in rat hypothalamus in an acute stress model. Moreover,

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several acute and chronic stress models showed increased histamine turnover (Ito, 2000). These seemingly discordant results show that animal models may insufficiently elucidate key aspects of the etiology and pathophysiology of depression (Neumann et al., 2011). Systematic validation of animal model results on patients and human material is thus necessary.

To the best of our knowledge, there has been no report so far of altered HMT in the MDD brain. The histamine degradation requires, however, the co-enzyme S-adenosyl-methionine (SAMe) as methyl donor (Haas et al., 2008). We have noted that various studies indicated that the administration of SAMe, a major methyl-donor for the synthesis of brain amines and maintenance of phospholipid cell membranes can be an effective treatment strategy for MDD patients (Nelson, 2010), while low levels of SAMe are present in the cerebrospinal fluid of severely depressed patients (Bottiglieri et al., 1990). Whether the lower HMT-mRNA in MDD we observed may be related to the generally lower level of methylation of histamine warrants further confirmation.

A positron emission tomography study in 10 age-matched controls and 10? MDD subjects showed that H_1R binding was much lower in the frontal, temporal and occipital cortex, and in the cingulate gyrus of depressed patients than in those structures in controls (Kano et al., 2004). In contrast, our study showed that the H_1R-mRNA expression level was unchanged in depression. It should be noted that we studied two other brain areas, i.e. the ACC (Brodman 24) and the DLPFC (Brodman 9), while Kano et al. (2004) studied the cingulate gyrus (Brodman 32) and PFC (Brodman 10 and 44). An alternative explanation for the discrepancy may be the age difference. In our study the subjects are much older (mean $\pm$ SD in DLPFC 73 ± 12 years of age and in ACC 75 ± 14 years of age) than in the Kano et al. (2004) study (41 ± 12 years of age). The unchanged H_3R-mRNA expression in the DLPFC in MDD and BD is in agreement with recent H_3R radioligand binding assays in postmortem PFC (Jin et al., 2009).

Abundant experimental data show that the neuronal histaminergic system plays a key role in sleep–wake regulation (Haas et al., 2008). At present it is not clear, however, whether alterations in the histaminergic system–or rather in the circadian system (Zhou et al., 2001)–are of primary importance where the lack of day–night fluctuations in depression is concerned. Further studies with larger samples and systematic circadian time points are warranted to study this point.

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Conflict of interest

None.

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