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Chapter 8

Unchanged histaminergic system in depression

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Abstract
Rodent experiments suggested that the neuronal histamine system may be involved in symptoms of depression. We determined, therefore, in post-mortem tissue the expression of the rate-limiting enzyme for histamine production and histidine decarboxylase in the tuberomamillary nucleus (TMN) using quantitative in situ hybridization, and qPCR to determine the expression of the four histamine receptors and of the enzyme breaking down histamine, histamine N-methyltransferase, in the prefrontal cortex (PFC). However, no changes were observed in the expression of these molecules: the neuronal histaminergic system seems to remain mostly intact in depression.

Keywords: Histaminergic system; Depression; Tuberomamillary nucleus; Postmortem prefrontal cortex

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, that are known to have a hyperactive stress systems (Bao et al., 2005).

2. Methods
2.1. Postmortem brain material
Patients with major depressive disorder (MDD) and bipolar disorder (BD) as well as matched controls were studied. All postmortem tissues were obtained through the Netherlands Brain Bank (NBB) following permission for a brain autopsy and for the use of brain material and clinical data for research purposes obtained by the NBB from patients or their next of kin. 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 clinico-pathological information on patients and matched controls see Supplementary Table 1. Neuropathological diagnosis were confirmed by systematic neuropathological analyses 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 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).

2.3. Quantitative PCR (qPCR) study in the frozen PFC and ACC tissue
In addition, the mRNA expression of the four histamine receptors $H_1 - H_4$ 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).

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). Due to the 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 H1-4R and of HMT of mood disorder patients and matched controls (P ≥ 0.117) did not differ significantly either in DLPFC or ACC. Unaltered histaminergic gene expressions in ACC or DLPFC were also observed in both MDD and BD with their matched controls (P ≥ 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, either in the rate limiting enzyme involved in its production or in its receptors and breaking-down enzyme in two 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 indicate 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, several acute and chronic stress models showed increased histamine turnover (Ito, 2000). These seemingly discordant results shows 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.

A positron emission tomography study showed that in 10 age-matched controls and MDD subjects H1R 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 H1R-mRNA expression level was unchanged in depression. It should be noted that two other brain areas we studied, the ACC (Brodman 24) and the DLPFC (Brodman 9), did not show the significantly lower H1R binding that Kano et al. (2004) observed in the cingulate gyrus (Brodman 32) and PFC (Brodman 10 and 44). An alternative explanation for the difference may be the age difference. In our study the subjects are much older (mean ± SD in DLPFC 73 ± 12 years of age and in ACC 75 ± 14 years of age) than in the Kano et al. (2004) study (mean ± SD 41 ± 12). The unchanged H3R-mRNA expression in the DLPFC in MDD and BD is in agreement with recent H3R 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 lar-
ger samples and systematic circadian time points are warranted to confirm our results.

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The sponsors did not contribute to the study design, nor to the collection, analysis and interpretation of data, the writing of the report or the decision to submit the paper for publication.

**Conflict of interest**

None

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