Psychoneuroendocrinology (2013) 38, 863—870

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Aberrant stress hormone receptor balance in the human prefrontal cortex and hypothalamic paraventricular nucleus of depressed patients

Xin-Rui Qi [a,b], Willem Kamphuis [a], Shanshan Wang [c], Qian Wang [d], Paul J. Lucassen [d], Jiang-Ning Zhou [b], Dick F. Swaab [a,*]

[a] *Netherlands Institute for Neuroscience, An Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands*
[b] *CAS Key Laboratory of Brain Function and Diseases, School of Life Sciences, University of Science and Technology of China, Chinese Academy of Sciences, Hefei, Anhui, PR China*
[c] *Department of Neurology, Clinical Division of Nanlou, Chinese PLA General Hospital, Beijing, China*
[d] *Center for Neuroscience, Swammerdam Institute of Life Sciences, University of Amsterdam, The Netherlands*

Received 14 June 2012; received in revised form 29 August 2012; accepted 16 September 2012

KEYWORDS
Anterior cingulate cortex;
Bipolar disorder;
Dorsolateral prefrontal cortex;
Mineralocorticoid receptor;
Major depressive disorder;
Paraventricular nucleus

Summary The prefrontal cortex (PFC) plays an important role in the regulation of the hypothalamo-pituitary-adrenal (HPA)-axis regarding stress response and possibly also depression. We used quantitative real-time PCR to determine the mRNA levels of 17 stress-related genes in the human postmortem anterior cingulate cortex (ACC) and dorsolateral PFC (DLPFC) of patients with mood disorder and of well-matched controls. The correlation between the expression of these DLPFC genes and their earlier measured expression in the paraventricular nucleus (PVN) of the same subjects was also determined. Transcript level of mineralocorticoid receptor (MR) was significantly decreased, while the ratio of glucocorticoid receptor (GR) α to MR mRNA level was increased in the ACC/DLPFC, both in the bipolar and major depressive disorder subgroups and also in the pooled depression group. Significantly inverse correlations were found for MR mRNA level and for GRα/MR ratio between the DLPFC and PVN. A selective disturbance of MR and of the GRα/MR ratio thus seems to exist in the ACC/DLPFC in depression, which was inversely correlated with the corresponding levels in the PVN. These changes may contribute to HPA-axis hyperactivity and hence to depression etiology.
© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Hypothalamo-pituitary-adrenal (HPA)-axis activity is dysregulated in a significant percentage of patients with bipolar disorder (BPD) and major depressive disorder (MDD), as

* Corresponding author at: Netherlands Institute for Neuroscience, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands. Tel.: +31 20 566 5500; fax: +31 20 566 6121.
E-mail address: d.f.swaab@nin.knaw.nl (D.F. Swaab).

0306-4530/$ — see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psyneuen.2012.09.014

evidenced by clinical and preclinical studies (Holsboer, 2001; Schule et al., 2009). Even on their own, individual hormones of the HPA-axis, such as corticotropin-releasing hormone (CRH) or cortisol, can induce symptoms of depression (Bao and Swaab, 2010). The importance of the hypothalamus in depression is further supported by the observation that ventral diencephalic volumes, mainly those including the hypothalamus, are among the strongest endophenotypes of depression (Glahn et al., 2012). HPA-axis activity and its subsequent response to stress are modulated by a complex network of brain structures and circuits, including the hippocampus, amygdala, prefrontal cortex (PFC) and anterior cingulate cortex (ACC) (Dedovic et al., 2009). These brain areas express corticosteroid receptors to mediate negative feedback regulation of the HPA-axis, which is suggested to be impaired in depression (Holsboer, 2000). Moreover, the regulatory role of the ACC/PFC can be stimulatory or inhibitory, depending on specific ACC/PFC subregions or stressor types (Dedovic et al., 2009). Together with the dysfunctioning ACC/PFC as shown by functional and structural imaging in depression (Drevets et al., 2008a,b), all available evidence indicates an abnormal interaction between the ACC/PFC and HPA-axis activity with possible implications for the pathogenesis of depression (Swaab et al., 2000; Dedovic et al., 2009).

Previously, we have shown that in the hypothalamic paraventricular nucleus (PVN) of depressed patients significant changes are present in several key stress-related genes, including CRH, CRH receptors (CRHRs), corticosteroid receptors and sex hormone receptors (Raadsheer et al., 1995; Wang et al., 2008). In the present study we investigated in the ACC/PFC whether the expression of CRH or associated factors modulating the network involved in stress regulation is changed in depression. We determined — in grey matter isolated from postmortem ACC and dorsolateral PFC (DLPFC) tissue of a clinically and neuropathologically well-characterized cohort of depressed patients and well-matched controls — the gene expression level of these molecules by quantitative real-time PCR (qPCR). In addition, we correlated the DLPFC stress-related molecules determined in the present study with those determined in the PVN from 11 overlapping subjects in our previous study (Wang et al., 2008).

2. Methods

2.1. Subjects

Postmortem brain specimens from elderly non-suicide depressed patients (DEP) and their matched controls without a psychiatric or neurological disease, as described before (Zhao et al., 2012), were obtained from the Netherlands Brain Bank (NBB), with informed written consent from the patients or their next of kin for the autopsy and use of brain material and clinical files for research purposes. The DEP patients were clinically diagnosed in various Dutch psychiatric hospitals with either BPD or MDD on the basis of the presence and severity of their symptoms and with the exclusion of other psychiatric and neurological disorders, which were systematically scored and confirmed by three qualified psychiatrists (Drs. W.J.G. Hoogendijk, E. Vermetten and G. Meynen) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, using the extensive medical records of the NBB. Systematic neuropathological investigation confirmed the absence of neuropathological changes in all subjects (Van de Nes et al., 1998). Depressed patients and controls were one-by-one matched for sex and group-matched for age, postmortem delay (PMD), clock time and month of death, cerebrospinal fluid (CSF)-pH and brain weight. The samples were obtained from the ACC (Brodmann area 24) of 12 DEP patients (sex, 9M/3F; age, 74.7 ± 3.9 (mean $\pm$ SEM)) and 12 matched controls (9M/3F; 79.5 ± 3.0) and DLPFC (Brodmann area 9) of 14 DEP patients (10M/4F; 72.8 ± 3.1) and 14 matched controls (10M/4F; 74.6 ± 3.0). Detailed clinicopathological information is shown in supplementary material (SM) 2.

Grey matter containing all six layers was isolated from 50 μm thick cryostat sections cut from snap-frozen ACC/DLPFC tissue as described before (Bossers et al., 2010).

2.2. Quantitative real-time PCR

RNA isolation, cDNA synthesis and qPCR reactions were performed as described (Wang et al., 2008; Zhao et al., 2012). RNA integrity value (RIN), an indicator of isolated RNA quality, was determined and no difference was found between the DEP and control groups (for ACC of the DEP group: 7.3 ± 0.2 and control: 7.2 ± 0.3; for DLPFC of the DEP group: 7.5 ± 0.2 and control: 7.7 ± 0.2, mean $\pm$ SEM, see SM3). Primer information for the target genes and reference genes are given in SM4. For qPCR analysis, the absolute amount of target genes was calculated by $10^{10} \times E^{-Ct}$ ($E = 10^{-(1/slope)}$) (Kamphuis et al., 2001). The geNorm analysis allows us to determine how many and which of the stable housekeeping genes from the seven candidates (glyceraldehyde-3-phosphate dehydrogenase (GAPDH), actin-β (ACTβ), hypoxanthine phosphoribosyltransferase 1 (HPRT1), ubiquitin C (UBC), tubulin-α (TUBα), tubulin-β4 (TUBβ4), hydroxymethylbilane synthase (HMBS)) we should use to control for unspecific and non-disease related changes, in either ACC or DLPFC. After the geNorm analysis, the geomean of the absolute amount of the following genes was calculated as reliable normalization factors, which did not differ between the diagnostic groups and their controls: GAPDH, ACTβ, HPRT1, UBC, TUBα, TUBβ4 for the ACC study and GAPDH, ACTβ, HMBS, HPRT1, TUBα, TUBβ4 for the DLPFC study. The following target genes were selected: CRH, urocortin3 (UCN3), CRHR1/2 (mediating CRH or UCN3 signal), CRH binding protein (CRHBP, controlling free CRH concentration), mineralocorticoid receptor/glucocorticoid receptor (MR/GR, mediating negative feedback on HPA-axis activity), estrogen receptor/androgen receptor (ER/AR, positively or negatively regulating CRH/UCN3 expression), cAMP-response element-binding protein (CREB, regulating CRH expression), interleukin-1β and tumor necrosis factor-α (IL1β and TNFα, associated with GR function), heat shock protein 70 and 90 (HSP70 and 90, determinants of glucocorticoid resistance), vasopressin receptor-1α (AVPR1α, a receptor for vasopressin which functions together with CRH during stress). The ratios between the respective receptor pairs, indicative of their balance, were also calculated, i.e. CRHR1/CRHR2, ER1/AR, ER1/ER2 and GRα/MR (stimulatory/inhibitory effects on HPA-axis activation. Their imbalance may lead to depression; Wang et al., 2008). For further details see SM1. The absolute

Download English Version:

https://daneshyari.com/en/article/10306240

Download Persian Version:

https://daneshyari.com/article/10306240

Daneshyari.com