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Brain serotonin 4 receptor binding is associated with the cortisol awakening response

Gustav R. Jakobsen[a,b], Patrick M. Fisher[a], Agnete Dyssegaard[a], Brenda McMahon[a,b,d], Klaus K. Holst[e], Szabolcs Lehel[c], Claus Svarer[a], Peter S. Jensen[a], Gitte M. Knudsen[a,b], Vibe G. Frokjaer[a,d,*]

[a] Neurobiology Research Unit and Center for Integrated Molecular Brain Imaging, DK-2100 Copenhagen, Denmark
[b] Faculty of Health and Medical Sciences, University of Copenhagen, DK-2100 Copenhagen, Denmark
[c] PET and Cyclotron Unit, DK-2100 Copenhagen, Denmark
[d] Psychiatric Center Copenhagen, Copenhagen University Hospital, Rigshospitalet, DK-2100 Copenhagen, Denmark
[e] Department of Biostatistics, University of Copenhagen, DK-1014 Copenhagen, Denmark

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ABSTRACT

Serotonin signalling is considered critical for an appropriate and dynamic adaptation to stress. Previously, we have shown that prefrontal serotonin transporter (SERT) binding is positively associated with the cortisol awakening response (CAR) (Frokjaer et al., 2013), which is an index of hypothalamic–pituitary–adrenal (HPA)-axis output dynamics. Here, we investigated in healthy individuals if cerebral serotonin 4 receptor (5-HT4r) binding, reported to be a proxy for serotonin levels, is associated with CAR.

Thirty healthy volunteers (25 males, age range 20–56 years) underwent 5-HT4r PET imaging with [^{11}C]-SB207145, genotyping of the SERT-linked polymorphic region (5-HTTLPR), and performed serial home sampling of saliva (5 time points from 0 to 60 min from awakening) to assess CAR. The association between 5-HT4r binding in 4 regions of interest (prefrontal cortex, anterior cingulate cortex, pallidostriatum, and hippocampus) and CAR was tested using multiple linear regression with adjustment for age and 5-HTTLPR genotype. Finally, an exploratory voxel-based analysis of the association was performed.

CAR was negatively associated with 5-HT4r binding in pallidostriatum ($p = 0.01$), prefrontal cortex ($p = 0.03$), and anterior cingulate cortex ($p = 0.002$), respectively, but showed no association in hippocampus. The results remained significant when taking into account other potentially relevant covariates.

In conclusion, our finding reinforces an association between HPA-axis function and serotonin signaling in vivo in humans. We suggest that higher synaptic serotonin concentration, here indexed by lower 5-HT4r binding, supports HPA-axis dynamics, which in healthy volunteers is reflected by a robust CAR.

1. Introduction

1.1. Serotonin signalling and stress

Serotonin brain signalling is considered critical to an appropriate and dynamic adaptation to stress through control of limbic system functions, which includes hypothalamic–pituitary–adrenal (HPA) axis activity (Puig and Gulledge, 2011). In general, acute stress enhances serotonin output, and in turn, serotonin signalling influences the secretion of corticosteroids (Lanfumey et al., 2008). Several studies suggest that serotonergic tone and stress responses are intimately related; (1) Acutely increased serotonin signalling increases the production of cortisol (Bhagwagar et al., 2002), (2) Serotonergic tone in the medial prefrontal cortex modulates behavioural stress responses by inhibitory actions in rats (Forster et al., 2008), (3) Lowering synaptic serotonin, by dietary depletion of its precursor tryptophan, in post-traumatic stress disorder patients who recovered on selective serotonin reuptake inhibitors (SSRIs) heightens their response to trauma-related stressors, which again strongly implicates a connection between low serotonin levels and disproportional stress reactivity (Corchs et al., 2009), (4) A large body of evidence supports a gene by environment link

* Corresponding author at: Neurobiology Research Unit 6931, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Fax: +45 356713.
E-mail address: vibe@nru.dk (V.G. Frokjaer).

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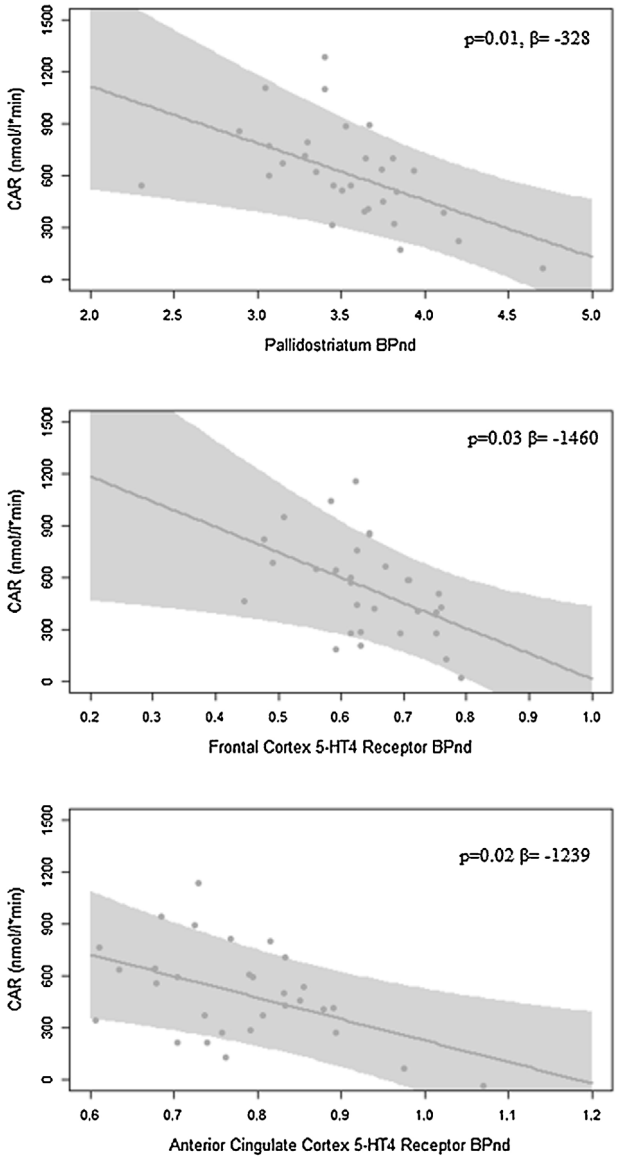

Fig. 1. Scatterplot of the association between 5-HT4r binding and cortisol awakening responses (CAR) adjusted for age and 5-HTTLPR genotype in pallidostriatum (top), prefrontal cortex (middle) and anterior cingulate cortex (bottom). Best fit line and 95% confidence interval are indicated with line and shading.

between serotonin and vulnerability to stress, which is possibly established already early in neurodevelopment; carriers of the low-expressing variants of the serotonin transporter gene (5-HTTLPR) are at greater risk of developing major depression when exposed to stressful environments (Caspi et al., 2010), (5) Also, in vivo brain levels of the serotonin transporter (SERT), which is a key regulator of synaptic serotonin and a marker of serotonergic neurons and their projections, is positively associated with HPA-axis dynamics in terms of the cortisol awakening response (CAR), as shown and replicated recently by our group (Frokjaer et al., 2013, 2014), and finally, (6) The majority of antidepressants target serotonin signalling and, notably, normalization of the HPA-axis in response to treatment is critical to the efficacy in terms of avoiding relapse (Ruhé et al., 2015; Schüle, 2007).

1.2. HPA-axis dynamics and mental health

A well-functioning and dynamic HPA-axis is critical for coping with everyday life stressors and for maintenance of mental health. One way to characterise the HPA-axis is by assessment of the cortisol awakening response (CAR), which is a superimposition on the circadian rhythm of cortisol release occurring in response to the transition from sleep to wakefulness (Wilhelm et al., 2007). CAR thus indexes HPA-axis dynamics considered relevant for a flexible response and a healthy adaptation to stressors. Importantly, it can be assessed by home-sampling of saliva, which does not in itself introduce stress. The HPA-axis output is regulated by the limbic system and associated areas including amygdala, hippocampus, prefrontal and anterior cingulate cortex (Pruessner et al., 2010). The neural output of these brain regions are integrated in the paraventricular nucleus of hypothalamus, which regulates corticotrophin release and ultimately cortisol secretion. Both hippocampus and prefrontal cortex express glucocorticoid and mineralocorticoid receptors and mediate negative feedback from circulating cortisol.

A meta-analysis point to a positive association between CAR and psychosocial factors such as job stress and general life stress within the healthy spectrum and, conversely, a negative association with more extreme conditions such as burn-out, fatigue and exhaustion (Chida and Steptoe, 2009). HPA-axis dysregulation is a prominent feature of major depressive disorder. Also HPA-axis