Progress in Neuropsychopharmacology & Biological Psychiatry 81 (2018) 88–95

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

A Homer 1 gene variant influences brain structure and function, lithium effects on white matter, and antidepressant response in bipolar disorder: A multimodal genetic imaging study

Francesco Benedetti[a,*], Sara Poletti[a,b], Clara Locatelli[a], Elena Mazza[a], Cristina Lorenzi[a], Alice Vitali[a], Martina Riberto[a], Silvia Brioschi[a,b], Benedetta Vai[a], Irene Bollettini[a], Elisa Melloni[a], Veronica Aggio[a], Andrea Falini[b,c], Andrea De Bartolomeis[d], Cristina Colombo[a,b]

[a] Psychiatry and Clinical Psychobiology, Division of Neuroscience, Scientific Institute Ospedale San Raffaele, Milano, Italy
[b] University Vita-Salute San Raffaele, Milano, Italy
[c] Neuroradiology Unit, Division of Neuroscience, Scientific Institute Ospedale San Raffaele, Milano, Italy
[d] Laboratory of Molecular and Translational Psychiatry, Unit of Treatment Resistant Psychosis, Section of Psychiatry, University Federico II, Napoli, Italy

ARTICLE INFO

Keywords:
Bipolar disorder
Depression
Glutamate
Homer
Antidepressant
Brain imaging
Grey matter
White matter
fMRI

ABSTRACT

Background: The Homer family of postsynaptic scaffolding proteins plays a crucial role in glutamate-mediated synaptic plasticity, a phenotype associated with Bipolar Disorder (BD). Homer is a target for antidepressants and mood stabilizers. The AA risk genotype of the Homer rs7713917 A > G SNP has been associated with mood disorders and suicide, and in healthy humans with brain function. Despite the evidence linking Homer 1 gene and function to mood disorder, as well as its involvement in animal models of depression, no study has yet investigated the role of Homer in bipolar depression and treatment response.

Methods: We studied 199 inpatients, affected by a major depressive episode in course of BD. 147 patients were studied with structural MRI of grey and white matter, and 50 with BOLD functional MRI of emotional processing. 158 patients were treated with combined total sleep deprivation and light therapy.

Results: At neuroimaging, patients with the AA genotype showed lower grey matter volumes in medial prefrontal cortex, higher BOLD fMRI neural responses to emotional stimuli in anterior cingulate cortex, and lower fractional anisotropy in bilateral frontal WM tracts. Lithium treatment increased axial diffusivity more in AA patients than in G*carriers. At clinical evaluation, the same AA homozygotes showed a worse antidepressant response to combined SD and LT.

Conclusions: rs7713917 influenced brain grey and white matter structure and function in BD, long term effects of lithium on white matter structure, and antidepressant response to chronotherapeutics, thus suggesting that glutamatergic neuroplasticity and Homer 1 function might play a role in BD psychopathology and response to treatment.

1. Introduction

Bipolar Disorder (BD) is associated with impaired synaptic function, cellular resilience and plasticity (Machado-Vieira et al., 2013). Factors affecting neuronal plasticity and glutamatergic neurotransmission could play a role in pathophysiology and treatment response in BD (Duman and Aghajanian, 2012; Lener et al., 2016), and could provide new treatment targets and translational models (Zarate et al., 2013).

The Homer family of scaffolding proteins, mainly located in the postsynaptic density (PSD) at glutamatergic excitatory synapses, plays a crucial role in the glutamate-mediated synaptic plasticity by binding metabotropic glutamate receptors type I (mGluRs1 and mGluR5), inositol-1,4,5-triphosphate (IP3) receptors, the NMDA glutamate receptor scaffolding protein Shank, and other elements involved in synaptic development and plasticity (de Bartolomeis and Tomasetti, 2012; Szumlinski et al., 2006). Homer proteins are encoded by three genes, among which the Homer 1 gene (located at chr. 5q14.2) evolved bimodal expression of constitutive and immediate early gene (IEG) products. All three isoforms might impact mood disorders psychopathology by influencing postsynaptic signaling transduction, critical for normal psychomotor and cognitive function. Widely expressed in brain excitatory and inhibitory neurons, the short isoform (Homer1a) is an

* Corresponding author at: Psychiatry and Clinical Psychobiology, Division of Neuroscience, Ospedale San Raffaele, San Raffaele Turro, Via Stamira d'Ancona 20, 20127 Milano, Italy.
E-mail address: benedetti.francesco@hsr.it (F. Benedetti).

http://dx.doi.org/10.1016/j.pnpbp.2017.10.011
Received 12 July 2017; Received in revised form 28 September 2017; Accepted 21 October 2017

immediate early gene whose expression is very low in resting animals, but rapidly increases after neuronal activity (Imamura et al., 2011). It supports the circadian synaptic homeostatic cycle, with potentiation during learning and memory and remodeling during sleep (Diering et al., 2017), a mechanism associated with changes of brain neuroplasticity underpinning antidepressant response in BD (Canali et al., 2014). The long form (Homer1b/c) is constitutively expressed, participates in maintaining dendritic spine structure and synaptic function, and is one of the putative targets mediating the neuroprotective effects of the mainstay mood stabilizers lithium and valproate (de Bartolomeis et al., 2012; Jiang et al., 2016).

In mice, deletion/downregulation of Homer 1 enhances anxiety- and depression-related behaviors, and increases endocrine and behavioral response to stressors, which are normalized after restoration of Homer1a in the frontal cortex (Lominac et al., 2005; Szumlinski et al., 2005; Wagner et al., 2015); moreover, chronic stress reduces Homer expression (Orsetti et al., 2008). Several antidepressant treatments including imipramine, fluoxetine, ketamine, electroconvulsive shock, transcranial magnetic stimulation, photic stimulation, and sleep deprivation (SD) inhibit depressive-like behaviors via induction of Homer1 in several brain structures (Conti et al., 2007; Dell'aversano et al., 2009; Serchov et al., 2015; Sun et al., 2011; Sun et al., 2015). Homer1 induction has then been proposed as a crucial joint mechanism for antidepressant therapy (Serchov et al., 2016).

In humans, association studies suggested a role for gene variants of Homer 1 in susceptibility to mood disorders and response to antidepressant treatments. In a genome-wide association study (GWAS) with two independent replication samples, Homer 1 single nucleotide polymorphisms (SNPs) were consistently included in clusters predicting antidepressant response in samples of patients mainly affected by Major Depressive Disorder (MDD 94%, BD 6%) (Ising et al., 2009). A GWAS study with a replication sample associated the AA risk genotype of an A > G SNP, located in a putative regulatory region approximately 20 kb upstream of the Homer 1 transcriptional start site (rs7713917), with (a) the diagnosis of MDD; and (b) in healthy humans, an increased prefrontal activation at functional magnetic resonance imaging (fMRI) at a working memory task, a reduced cingulate fMRI activation during a reward task, and slower reaction times at an emotional face-matching task (Rietschel et al., 2010). In two more studies, the same rs7713917 AA genotype was also associated with childhood-onset mood disorders (Strauss et al., 2012), and with increased alcohol consumption in adolescents (Heinrich et al., 2016), while other Homer 1 gene variants, also in the same linkage disequilibrium block of rs7713917, were associated with suicidal behaviors (Rao et al., 2016; Rao et al., 2017; Strauss et al., 2012).

These Homer 1 gene variants were never specifically studied in patients affected by BD, neither correlated with treatment response. With a multimodal approach, here we studied the effect of rs7713917 on brain grey and white matter structure and function, on depressive symptomatology, and on antidepressant response to chronotherapeutics (combined sleep deprivation and light treatment) in patients with BD.

2. Methods

2.1. Participants

We studied 199 consecutively admitted caucasian inpatients of Italian descent affected by a major depressive episode, without psychotic features, in course of Bipolar Disorder type I (DSM IV-TR criteria). Inclusion criteria were: to be willing to participate; absence of other diagnoses on Axis I, pregnancy, history of epilepsy, major medical and neurological disorders; absence of a history of drug or alcohol dependency or abuse within the last six months. Physical examinations, laboratory tests and electrocardiograms were performed at admission. Severity of depression was rated on 6-item version of the Hamilton Depression Rating Scale (HDRS-6) (Bech et al., 1975). Imaging was performed on a 3.0 Tesla scanner (Gyroscan Intera, Philips, Netherlands). After complete description of the study to the participants, a written informed consent was obtained. All the research activities were approved by the local ethical committee.

2.2. Genotyping

Genomic DNA was extracted from leukocytes by NaCl precipitation (Lahiri and Nurnberger, 1991) (Supplementary methods). To identify rs7713917, a polymerase chain reaction (PCR) was performed using the following primers: 5′ CTCACTCAACCCATAACAACCC 3′ (forward), 5′ GCATCCTAATCCTGCTACCCA 3′ (reverse). An aliquot of purified PCR product was then used to perform sequencing reaction, and its products were sequenced with a 48 capillaries genetic analyzer (MegaBace500, GE Healthcare, Milan, Italy).

Due to the relatively lower number of homozygote rs7713917 GG participants, and in the light of previous literature (Rietschel et al., 2010; Strauss et al., 2012), we pooled them with heterozygote carriers of the A allele thus comparing rs7713917 AA homozygotes and rs7713917 *G carriers.

2.3. Treatment

158 patients were administered three consecutive SD cycles (day 0–7). Each cycle was composed of a period of 36 h awake. Following an established protocol (Benedetti et al., 2005; Benedetti et al., 2014), patients were totally sleep deprived on days 1, 3, and 5 from 07:00 until 19.00 of the following day. They were then allowed to sleep during the nights of days 1, 3, and 5. Patients were administered LT (exposure for 30 min to a 10,000 lux bright white light, colour temperature 4600 K) at 03:00 a.m. during the SD nights and after awakening in the morning after recovery sleep. Patients were either taking lithium at admission, and continued it, or started lithium together with the chronotherapeutic procedure to enhance its effect and prevent relapse.

2.4. Voxel-based morphometry

Structural T1-weighted MRI scans (Supplementary methods) of 147 participants were processed with the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat), which is integrated in the SPM12 software package (Statistical Parametric Mapping, Institute of Neurology, London, UK). Voxel-based morphometry (VBM) statistics were carried out within the general linear model (GLM) framework, to compare GM volumes between AA subjects and G carriers. Age, sex, lithium treatment and total intracranial volume were added as nuisance covariates. We searched the whole brain for differences surviving a threshold, family-wise error (FWE) corrected for multiple comparisons, of $pFWE < 0.05$.

2.5. Functional MRI

Neural correlates of implicit emotional processing were investigated in 50 participants with a face matching paradigm (Hariri et al., 2002), which previously allowed to define the connectivity within the emotional circuitry in healthy controls and in patients affected by bipolar disorder and schizophrenia (Radaelli et al., 2014; Sladky et al., 2013; Vai et al., 2015), by presenting blocks of six pictures each representing human faces with fearful or angry expressions, interspersed with five blocks of six pictures of geometric shapes. Images were computed and analyzed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuroscience, Institute of Neurology and the National Hospital for Neurology and Neurosurgery; London, England). At the individual level, we compared (*t*-test, $p < 0.001$) the face-matching condition with the shape-matching condition, thereby isolating regions engaged in the emotional processing of faces. The single-subjects' contrast images were entered as dependent variables in