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Hippocampal neuroligin-2 links early-life stress with impaired social recognition and increased aggression in adult mice

Christine Kohl[a,b], Xiao-Dong Wang[b,c], Jocelyn Grosse[a], Céline Fournier[a], Daniela Harbich[b], Sören Westerholz[b], Ji-Tao Li[d], Alexandre Bacq[a], Claudia Sippel[b], Felix Hausch[b], Carmen Sandi[a,1], Mathias V. Schmidt[b,*,1]

[a] *Laboratory of Behavioral Genetics, Brain Mind Institute, School of Life Sciences, École Polytechnique Fédérale de Lausanne, EPFL, 1015 Lausanne, Switzerland*
[b] *Max Planck Institute of Psychiatry, Department of Stress Neurobiology and Neurogenetics, 80804 Munich, Germany*
[c] *Department of Neurobiology, Key Laboratory of Medical Neurobiology of Ministry of Health of China, Zhejiang Province Key Laboratory of Neurobiology, Zhejiang University School of Medicine, 310058 Hangzhou, China*
[d] *Institute of Mental Health, Peking University, No. 51 Hua Yuan Bei Road, 100191 Beijing, China*

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Summary Early-life stress is a key risk factor for the development of neuropsychiatric disorders later in life. Neuronal cell adhesion molecules have been strongly implicated in the pathophysiology of psychiatric disorders and in modulating social behaviors associated with these diseases. Neuroligin-2 is a synaptic cell adhesion molecule, located at the postsynaptic membrane of inhibitory GABAergic synapses, and is involved in synaptic stabilization and maturation. Alterations in neuroligin-2 expression have previously been associated with changes in social behavior linked to psychiatric disorders, including schizophrenia and autism. In this study, we show that early-life stress, induced by limited nesting and bedding material, leads to impaired social recognition and increased aggression in adult mice, accompanied by increased expression levels of hippocampal neuroligin-2. Viral overexpression of hippocampal neuroligin-2

* Corresponding author at: Max Planck Institute of Psychiatry, Department of Stress Neurobiology and Neurogenetics, Kraepelinstr. 2-10, 80804 Munich, Germany. Tel.: +49 89 30622 519; fax: +49 89 30622 610.
E-mail address: mschmidt@mpipsykl.mpg.de (M.V. Schmidt).
[1] Both authors contributed equally to this work.

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in adulthood mimics early-life stress-induced alterations in social behavior and social cognition. Moreover, viral knockdown of neuroligin-2 in the adult hippocampus attenuates the early-life stress-induced behavioral changes. Our results highlight the importance of neuroligin-2 in mediating early-life stress effects on social behavior and social cognition and its promising role as a novel therapeutic target for neuropsychiatric disorders.

1. Introduction

Neuronal cell adhesion molecules (nCAMs) are involved in regulating synapse function, synaptic properties and neurotransmission (Dalva et al., 2007; Sandi, 2004; Südhof, 2008). Neuroligins (nlgns) are postsynaptic type-I membrane proteins linking pre- and postsynaptic membranes by binding to presynaptic neurexins (nrxns) (Chih et al., 2005; Craig and Kang, 2007; Südhof, 2008). The nlgn family members are encoded by 4 genes in mammals, nlgn1-4, and appear in different postsynaptic specializations (Südhof, 2008). Nlgn1 and nlgn2 have been shown to be mainly localized in excitatory glutamatergic and inhibitory GABAergic synapses, respectively, while nlgn3 seems to be present in both and nlgn4 appears to be associated with glycinergic synapses (Budreck and Scheiffele, 2007; Hoon et al., 2011; Varoqueaux et al., 2004). Nlgns and nrxns contain an intracellular PDZ domain that interacts with scaffolding proteins and molecules linked to the intracellular machineries, including the cytoskeleton, vesicle exocytosis and receptor recruitment cascades (Dalva et al., 2007; Dean and Dresbach, 2006; Levinson and El-Husseini, 2005; Missler et al., 2003; Sandi, 2004). In particular, nlgn2 binds to the postsynaptic scaffolding protein gephyrin and to collybistin, which are involved in $GABA_A$-receptor recruitment; thus, nlgn2 may influence GABAergic synaptic properties (Chih et al., 2005; Chubykin et al., 2007; Poulopoulos et al., 2009; Varoqueaux et al., 2006).

Various studies indicate that synaptic dysfunction, arising from environmental and/or genetic factors that disturb developmental processes during early-life, is involved in the etiology of schizophrenia and autism (Betancur et al., 2009; Lewis and Levitt, 2002). Environmental challenges early in life have a decisive impact on the adult phenotype and one's individual risk to develop psychiatric disorders (McCrory et al., 2012; Meaney and Szyf, 2005; Schmidt et al., 2011). For example, childhood maltreatment and parental loss have been linked to adult major depression (Heim and Nemeroff, 2002), schizophrenia (Agid et al., 1999) and antisocial behavior (Widom and Brzustowicz, 2006). Importantly, early-life stress (ELS) has been shown to promote excessive and impulsive aggression, a key symptom of these psychiatric diseases (Dodge et al., 1990; Fonagy, 2004; Veenema, 2009). The early social environment, especially maternal care, seems to be essential for learning how to appropriately utilize aggression (Loeber and Hay, 1997; Tremblay et al., 2004; Veenema et al., 2006). ELS affects important developmental processes, including neurogenesis and synapse formation, and the long-term effects on structure and function of brain regions involved in modulating social behaviors, like the hippocampus, amygdala and prefrontal cortex, have been hypothesized to increase the risk for psychiatric diseases (Teicher et al., 2003). Emerging evidence especially implicates the hippocampus as being involved in modulating contextually adequate emotional behavior, social behavior, and aggression in addition to its role in cognitive functions (Kohl et al., 2013; Phillips et al., 2003; Sala et al., 2011; van der Kooij et al., 2013).

Stress-induced remodeling of neuronal networks involves breakdown and re-establishment of synapses, engaging nCAMs associated with synapse functioning and intracellular signaling (McEwen, 2012; Sandi, 2004). Mutations in nlgns have been implicated in the pathophysiology of autism and schizophrenia, which are characterized, among others, by altered social behavior, ranging from social withdrawal to excessive aggression (Larsson et al., 2005; Steinert et al., 1999; Sun et al., 2011). Shifts in nlgn2 expression levels have been shown to alter aggression-related behaviors as well as anxiety, exploration of novel stimuli and social behavior in animal models (Blundell et al., 2009; Hines et al., 2008; Kohl et al., 2013).

Since ELS is strongly associated with the development of neuropsychiatric disorders and nlgns are involved in modulating social behavior linked to the above mentioned diseases, we hypothesized that nlgns may directly mediate the effects of ELS on social behavior. In the present study, we investigated the impact of ELS on adult social behavior and the potential of viral overexpression and knockdown of nlgn2 in the adult hippocampus to mimic or attenuate, respectively, the alterations in social behavior induced by ELS.

2. Materials and methods

2.1. Animals

Experiment 1 was conducted on age-matched male C57Bl/6 mice derived from in-house breeding at the École Polytechnique Fédérale de Lausanne (EPFL, Lausanne, Switzerland; first batch = discovery cohort), the Max Planck Institute of Psychiatry (MPIP, Munich, Germany; second batch = replication cohort 1, see Supplemental Results) and the Institute of Mental Health (Peking University; third batch = replication cohort 2). Experiment 2 was conducted on age-matched male C57Bl/6 (age of arrival: 8 weeks) derived from Charles River Laboratories, France, and housed under EPFL conditions. Experiment 3 was performed on age-matched male C57Bl/6 derived from in-house breeding at the EPFL and were housed under respective conditions (see below).

All animals housed in the animal facility at the EPFL and the Institute of Mental Health were held under the following conditions: ventilated cages; 12 h light/dark cycle (lights on at 07:00 a.m.); temperature and humidity in the animal