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The stress-inducible actin-interacting protein DRR1 shapes social behavior

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Summary Understanding the molecular mechanisms by which stress is translated into changes in complex behavior may help to identify novel treatment strategies for stress-associated psychiatric disorders. The tumor suppressor gene down-regulated in renal cell carcinoma 1 (DRR1) was recently characterized as a new molecular link between stress, synaptic efficacy and behavioral performance, most likely through its ability to modulate actin dynamics.

The lateral septum is one of the brain regions prominently involved in the stress response. This brain region features high DRR1 expression in adult mice, even under basal conditions. We therefore aimed to characterize and dissect the functional role of septal DRR1 in modulating complex behavior. DRR1 protein expression was shown to be expressed in both neurons and astrocytes of the lateral septum of adult mice. Septal DRR1 mRNA expression increased after acute defeat stress and glucocorticoid receptor activation. To mimic the stress-induced DRR1 increase in the lateral septum of mice, we performed adenovirus-mediated region-specific

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overexpression of DRR1 and characterized the behavior of these mice. Overexpression of DRR1 in the septal region increased sociability, but did not change cognitive, anxiety-like or anhedonic behavior. The observed changes in social behavior did not involve alterations of the expression of vasopressin or oxytocin receptors, the canonical social neuropeptidergic circuits of the lateral septum.

In summary, our data suggest that the stress-induced increase of DRR1 expression in the lateral septum could be a protective mechanism to buffer or counterbalance negative consequences of stress exposure on social behavior.

1. Introduction

Stress evokes a plethora of physiological reactions used to optimize an individual's adaptation to changing demands. However, the molecular players translating stressful environmental stimuli into adaptive (*i.e.* beneficial) or maladaptive (*i.e.* adverse) consequences in neuronal function still remain largely unknown. These maladaptive consequences may predispose to the development of stress-associated psychiatric disorders in individuals at risk (De Kloet et al., 2005). Therefore, unraveling the underlying neurobiological mechanisms might open up the opportunity to identify new treatment strategies. Here, the identification of novel, yet unprecedented stress-regulated targets is of particular importance.

We recently identified a novel stress- and glucocorticoid-regulated gene, downregulated in renal cell carcinoma 1 (DRR1, also named Tu3A and Fam107A) in the mouse brain (Liebl et al., 2009; Schmidt et al., 2011). DRR1 was initially described to be a tumor suppressor gene (Wang et al., 2000; Yamato et al., 1999). Also, DRR1 expression is increased in post-mortem samples of the dorsolateral prefrontal cortex in patients with bipolar disorder and schizophrenia (Shao and Vawter, 2008), supporting its potential importance in the pathophysiology of mental disorders. The DRR1 gene is strongly conserved among species, showing 90% homology between mice and humans, and contains at least three functional glucocorticoid response elements. In the adult mouse brain, DRR1 shows a prominent mRNA expression in the cerebellum and in limbic areas such as the hippocampal CA3 region and the lateral septum (LS). Glucocorticoid receptor (GR) activation in mice induces DRR1 gene expression in stress-relevant brain regions such as the hypothalamic paraventricular nucleus (PVN) and the hippocampal CA3 region (Liebl et al., 2009; Schmidt et al., 2011). Interestingly, transcription of DRR1 was reported to exclusively require GR receptor homodimerization (Frijters et al., 2010).

We previously dissected in detail the role of DRR1 in the CA3 region of the hippocampus by virus-mediated overexpression *in vivo*. Mice with increased DRR1 expression in the CA3 region — thereby mimicking the stress-induced increase in hippocampal DRR1 — exhibited improved cognitive performance (Schmidt et al., 2011). We could provide further evidence that modulation of these complex behaviors by DRR1 was linked to its ability to specifically modulate actin dynamics and consequently, actin-dependent neurite outgrowth *in vitro*.

Besides the hippocampus, the LS is one of the most prominent expression sites of DRR1 in the adult mouse brain under basal conditions. The LS — which comprises the lateral, intermediate and ventral subdivisions (Alonso and Frotscher, 1989) — receives major input from the hippocampal region (Risold and Swanson, 1996) but also from other brain regions involved in cognitive (prefrontal cortex, entorhinal cortex) and affective (amygdala, hypothalamus, bed nucleus) function (Sheehan et al., 2004). The complex connectivity of the septal region confers a key role to the LS in integrating information and this may be the reason why the exact function of the LS is not yet fully understood. A large body of evidence supports its role in stress responses (Singewald et al., 2011), emotional processes (Calfa et al., 2007, 2006) and social behavior (Litvin et al., 2011). Given the ability of DRR1 to modulate hippocampus-dependent complex behavior, it is intriguing to ask whether septal DRR1 might play a role in modulating septum-dependent behavioral domains as well, such as social behavior. Vasopressin and oxytocin receptors are also highly expressed in the septum (Freund-Mercier et al., 1988) and play an important role in mediating stress response (Litvin et al., 2011; Neumann and Landgraf, 2012). Therefore a potential functional interaction between DRR1 and vasopressin and/or oxytocin receptors in the septum may account for changes in behavior.

In the present work we aimed to further dissect the functional role of DRR1 with a particular focus on the septal region. We first hypothesized that septal DRR1 gene expression is modulated by stress and glucocorticoids. We therefore characterized the cellular localization under basal conditions and the changes in DRR1 mRNA expression produced by stress and glucocorticoids. Second, we hypothesized that changes in septal DRR1 expression might significantly modulate complex behavior. To test this, we used an adeno-associated viral vector containing the DRR1 coding sequence to investigate the impact of increased DRR1 gene expression in the septum on different aspects of behavior. Our results point toward a specific modulatory role of septal DRR1 in shaping social behavior, and corroborate the importance of DRR1 as a molecular link between stressful experiences, protective neuronal adaptation processes and regulation of complex behavior.

2. Methods

2.1. Animals

Male C57Bl/6N mice (Charles River Laboratories, Germany; >12 weeks old) were used for all experiments. Animals were allowed to rest at least 1 week upon arrival before