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Research Report

Homer1a disruption increases vulnerability to predictable subtle stress normally sub-threshold for behavioral changes

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ABSTRACT

Homer1a is implicated in depression in humans and depression-like behavior in mice. To further understand the role of Homer1a in stress-induced emotional changes, we applied very mild stress to Homer1a knockout (H1a KO) mice. The wild-type (WT) and H1a KO mice were restrained for 2 h daily for 7 consecutive days at the same time of the day. The restraint was so mild that no changes in anxiety- or depression-like behavior were detected in either type of mice. However, total locomotion in the open field test and forced swimming test was increased by restraint in H1a KO mice only. After behavior, we made brain slices to examine neuronal excitability in cingulate cortex pyramidal cells and synaptic efficiency in hippocampal CA1 synapses. The excitability, assessed on the basis of the frequency of spikes elicited by current injection, was increased by restraint in H1a KO mice. The synaptic efficiency was evaluated by comparing the input–output relationship between the size of fiber volley and the slope of field excitatory postsynaptic potentials, and was shown to be increased by restraint in H1a KO mice only. Thus, predictable subtle stress, which failed to induce behavioral or electrophysiological changes in WT mice, resulted in a minor behavioral change that accompany upregulation of neuronal excitability and synaptic efficiency in H1a KO mice, suggesting that Homer1a may play a critical role in resilience to subtle stress.

1. Introduction

Homer1, a member of the scaffold protein family Homer, consists of the longer and shorter splice variants, Homer1b/c and Homer1a (Brakeman et al., 1997; Kato et al., 1997). Both variants bind to diverse receptors including metabotropic glutamate receptors (mGluRs). These receptors are cross-linked by self-multimerization of Homer1b/c, the longer constitutively-expressed variant. Homer1a, which lacks the multimerizing motif, is activity-dependently induced and prevents the cross-linkage by Homer1b/c multimerization.

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Homers are involved in a wide variety of neuropsychiatric abnormalities (Szumlinski et al., 2006). In particular, a genome-wide association study implicated Homer1 in pathogenesis of major depression (Rietschel et al., 2010). By using a modified version of the original forced swimming model of depression in mice, we have recently revealed that expression of Homer1a in the neocortex is decreased in depression model mice and recovered by imipramine application or repetitive transcranial magnetic stimulation (rTMS; Sun et al., 2011). Such Homer1a upregulation induced by rTMS is considered to constitute a part of negative feedback regulation of neuronal excitability, in which neural activity-induced Homer1a facilitates the large conductance calcium-activated potassium (big-K; BK) channel and thereby decreases excitability (Sakagami et al., 2005). Consistently, anti-epileptigenic effects of Homer 1a has been more directly demonstrated (Potschka et al., 2002; Klugmann et al., 2005).

To further elucidate the role played by Homer1a in depression, the present study relied upon two different approaches. First, chronic mild stress was adopted as the stressor, instead of forced swimming. The suitability of forced swimming as a stressor inducing depression-like behavior in rodents has been frequently in question (Holmes, 2003; Nestler and Hyman, 2010; Veenema et al., 2003). It has been considered that changes in animal behavior induced by acute intensive insults are less likely to represent human depression than those induced by chronic accumulation of mild stress (Holmes, 2003; Nestler and Hyman, 2010; Willner, 1997; Willner, 2005). In the present experiments, therefore, forced swimming was used only as a test paradigm detecting depressive states. Second, we used Homer1a knockout (KO) mouse (Inoue et al., 2009), in which constitutive expression of Homer1b/c is normal but activity-dependent expression of Homer1a is disrupted. By introducing these two modifications, we attempted to demonstrate an essential involvement of Homer1a in resilience to stressors.

2. Results

2.1. Behavior

In the open field test, there was an across-group difference in the total distance traveled among the 4 groups (Fig. 1a): wild-type (WT) and Homer1a-knockout (H1a KO) mice with or without restraint (WT-control, WT-restraint, H-control, H-restraint; one-way ANOVA, $F(3,95)=29.193$, $P=0.001$). The H-restraint group exhibited a reduced locomotion (9.62 ± 0.37 m; $N=26$) than WT-control group (13.29 ± 0.38 m, $N=25$; post hoc Tukey HSD test, $P=0.001$). Restraint increased the mobility in H1a KO mice (H-restraint; 11.17 ± 0.35 m, $N=24$, $P=0.031$), but not in WT mice (WT-restraint; 14.29 ± 0.45 m, $N=24$, $P=0.277$). However, among the 4 groups, there was no across-group difference in the time spent in the inner zone ($F(3,95)=1.530$, $P=0.212$), indicating that neither Homer1a disruption nor restraint induced anxiety-like tendency (Fig. 1b). This was confirmed by the light/dark test (Fig. 1c), in which no across-group difference was detected in the time spent in the light compartment

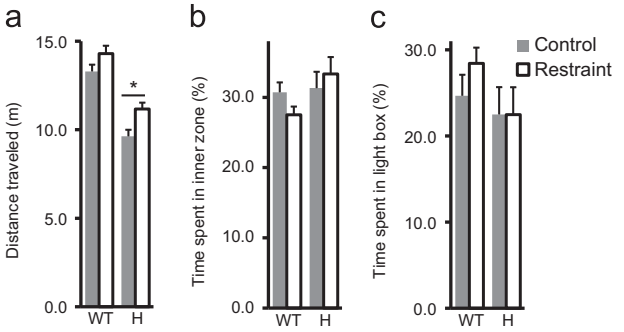

Fig. 1 – Test results evaluating anxiety-like behavior of WT and H1a KO mice. (a,b) Open field test results. The total distance traveled was increased by restraint in H1a KO mice only, but not WT mice (a). *, $P<0.05$. The time spent in the inner zone was not altered by restraint in H1a KO or WT mice (b). (c) The light/dark test results. Restraint did not alter the time spent in the light compartment in H1a KO or WT mice.

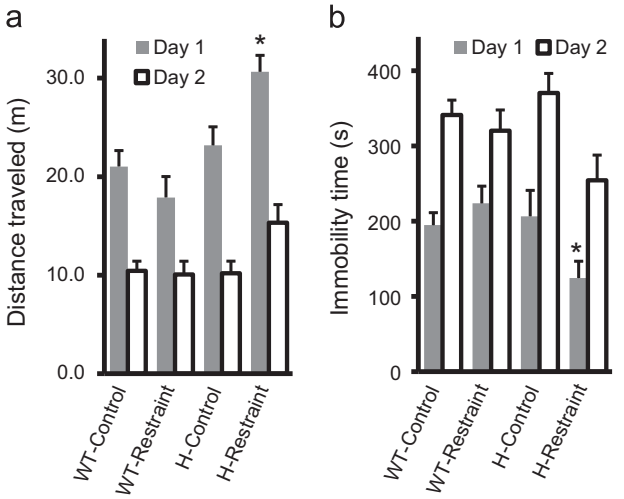

Fig. 2 – Forced swimming test results. In all the 4 experimental groups, the distance traveled (a) was shortened and the immobility time (b) elongated on Day 2 as compared with those on Day 1, confirming that depression-like behavior was similarly detected in all the groups, irrespective of whether restraint was imposed. Multiple comparisons revealed that the locomotor activity on Day 1, assessed by both measures (a,b), was higher in the H-restraint group than in any other groups. *, always $P<0.05$ as compared with the other 3 groups.

among the 4 groups (WT-control, 24.67 ± 2.44 s, $N=20$; WT-restraint, 28.42 ± 1.83 s, $N=19$; H-control, 22.5 ± 3.17 s, $N=26$; H-restraint, 22.47 ± 3.18 s, $N=24$; one-way ANOVA, $F(3,85)=0.893$, $P=0.448$).

Depression-like behavior was examined by the forced swimming test (Fig. 2). The distance swum on Day 2, as expressed by percent of that on Day 1, did not differ among the 4 groups (Fig. 2a; one-way ANOVA, $F(3,55)=0.369$, $P=0.776$). Neither did the immobility time on Day 2 as compared with Day1 (Fig. 2b; one-way ANOVA, $F(3,55)=1.206$, $P=0.312$), suggesting that restraint failed to induce