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Short Communication

Juvenile stress alters LTP in ventral hippocampal slices: Involvement of noradrenergic mechanisms

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HIGHLIGHTS

- Lasting impact of juvenile stress on LTP in ventral (VH)/dorsal hippocampus (DH).
- In adult rats, juvenile stress impaired LTP in DH, while it was facilitated in VH.
- Juvenile stress reversed a norepinephrine-mediated facilitation of LTP in DH vs. VH.
- Associated with increased expression of beta1-adrenergic receptor in VH but not DH.
- Thus, juvenile stress induces a lasting sensitivity to adrenergic modulation in VH.

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ABSTRACT

Childhood adversity is a prominent risk factor for developing stress-related disorders in adulthood. It can be modeled in rodents, where altered stress responses in adulthood have been observed. The ventral hippocampus is thought to be involved in emotional responses and displays a unique modulation of synaptic plasticity following exposure to stress. Here, we investigated the long-term effect of juvenile stress (at postnatal age of 27–29 days) on synaptic plasticity in the ventral and dorsal hippocampus of adult, 3 month old rats. The rats that had experienced juvenile stress expressed impaired LTP in the dorsal hippocampus (DH), while ventral hippocampus (VH) LTP was facilitated. Furthermore, juvenile stress caused reduced sensitivity to the beta-adrenergic agonist isoproterenol (Iso; 1 μM) in the adult DH, while it enhanced its action in VH slices. Further, juvenile stress resulted in an increase in the expression of beta1-adrenergic receptors in the VH but not in the DH, as revealed by western blot. Taken together, the ventral hippocampus expresses a lasting sensitivity to adrenergic modulation, thus likely to affect the emotional response to challenging situations in adulthood.

Childhood adversity is a well-known predisposing factor for developing depression and anxiety disorders later in life [1,2]. It can be modeled in rodents by submitting rats to brief variable and non-predictable stressors in their post-weaning to pre-pubertal life phase [3]. Such an exposure to juvenile stress (JS) results in anxiety-like behavior and impairs the rats' ability to cope with a variety of challenging situations in a sex-specific manner [4–6]. These behavioral alterations are associated with neurochemical and electrophysiological alterations in limbic brain areas such as amygdala and hippocampus [7,8] (for a review see [3]). It has been shown that JS affects the HPA axis, which is manifested in a long lasting increase in basal plasma levels of corticosterone (CORT) and altered hippocampal CORT receptor composition as well as in altered HPA axis response to additional emotional challenge in adulthood [6,9,10].

Recent studies suggest that CORT modulates synaptic plasticity along the septotemporal axis of the hippocampus in a differential manner [11,12]. In particular, while in the dorsal hippocampus

Abbreviations: β1AR and β2AR, beta 1 and beta 2 adrenergic receptors; Ct, control group; CORT, corticosterone; DH, dorsal hippocampus; NE, norepinephrine; Iso, isoproterenol; JS, juvenile stress; VH, ventral hippocampus.

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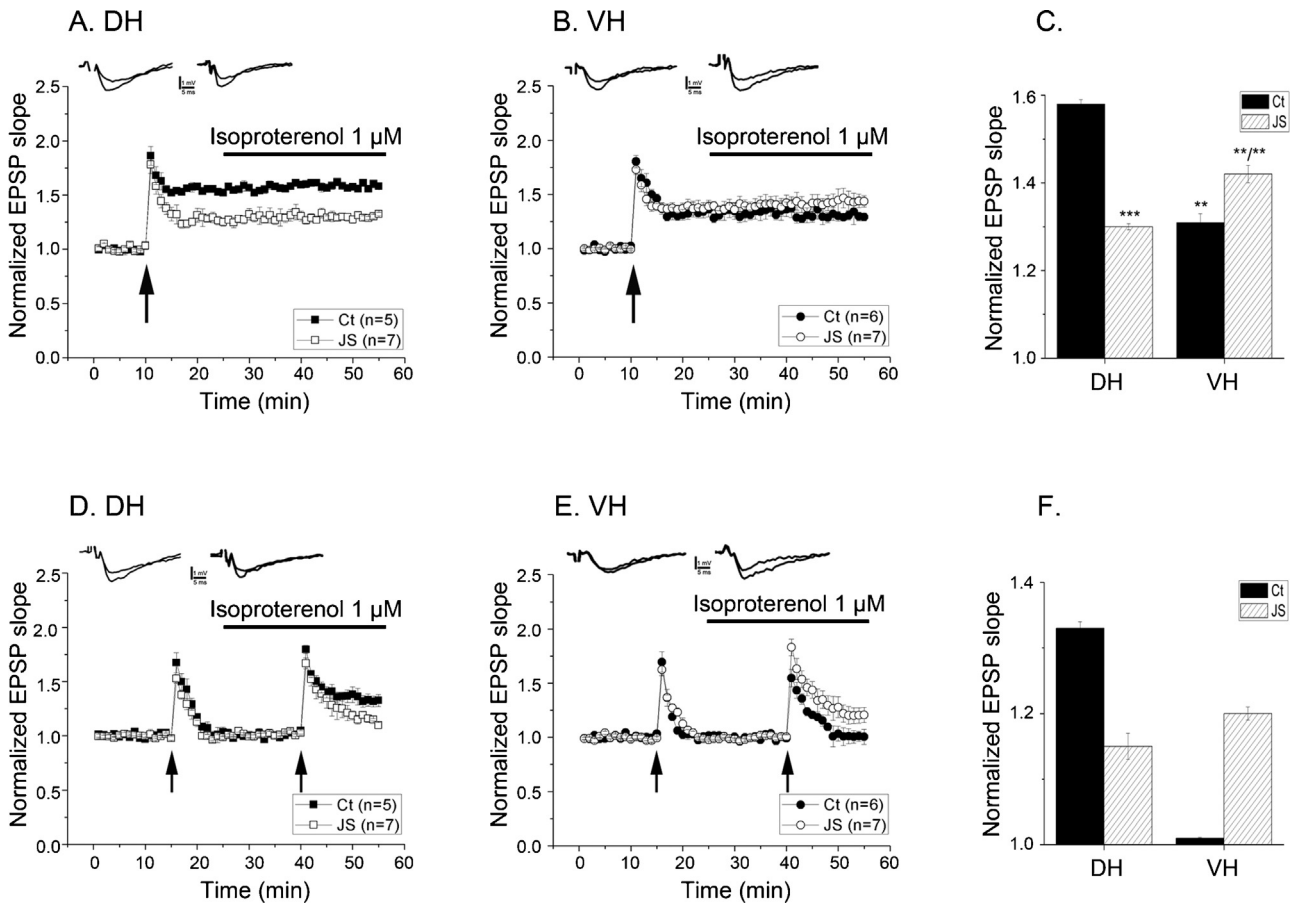

Fig. 1. Juvenile stress (JS) reduces LTP in DH and facilitates it in VH. A and B: LTP was induced by high-frequency stimulation, (HFS, 100 Hz, 1 s) at twice of the test intensity. The arrow denotes the point at which tetanic stimulation was delivered. VH slices express a significantly lower magnitude LTP than DH slices. Isoproterenol applied after the tetanic stimulation did not affect the already amplified responses. *C*: Summary bar graph of the results presented in A and B. JS significantly impairs LTP in DH and facilitates it in VH slices. It should be noted that the same slices presented in A are also used for the experiments in D, and B are the same slices as E. In both groups, one stimulating electrode was used for A and B and another for the slices presented in D and E. The results were presented in different sectors for simplicity of illustration. D and E: Tetanic stimulation, subthreshold to long-term potentiation (LTP) induction (35 pulses, 100 Hz), was delivered to the one pathway twice. The arrows denote the points at which weak tetanic stimulation was delivered. First stimulation produced a transient, short term potentiation (STP) in DH and VH of both Ct and JS groups. In the presence of isoproterenol (1 μM) the short tetanic stimulation now produces LTP in DH slices of Ct, but not in JS slices, and in VH slices of JS rats only. F: Summary diagram of the results shown in D and E. ** Significant differences at $p < 0.01$. *** Significant difference at $p < 0.001$, for both D and F.

(DH) LTP is suppressed by activation of glucocorticoid receptors, LTP is enhanced by activation of mineralocorticoid receptors in the ventral hippocampus (VH) [12].

Like CORT, norepinephrine (NE) is released during stress [13] and can serve to modulate hippocampal LTP [14–17]. Recently, we have demonstrated a NE-mediated conversion of short-term potentiation to LTP in normal DH CA1 but not in the VH. Surprisingly, this locus of action was switched from the DH to the VH following exposure to prenatal stress [18]. The present study was designed to extend these observations into the adult brain, and examine potential long-lasting effects of JS on synaptic plasticity in the DH and VH during adulthood and their modulation by NE.

All experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of the Weizmann Institute. Male Wistar rats, born and raised locally, were housed 4 per cage (22 ± 2 °C; light-dark cycle: 12/12 h, lights on at 7am with water and food ad libitum). Control (Ct) rats were left undisturbed in their home cage until three months of age. JS rats were exposed to a stress protocol [4] at PND 27–29, as follows: on day 27; 15 min of forced swim, day 28; 30 min on an elevated platform, day 29; 2 h of restraint in a narrow tube.

At three months of age, rats of both Ct and JS groups were sacrificed and their brains removed. One hippocampus was sliced for electrophysiology, while the contralateral hippocampus was used for biochemical analysis. Extracellular recordings of population EPSPs were made in the stratum radiatum of CA1 region of slices taken from the dorsal and ventral sectors of the hippocampus, as described before [18]. EPSPs were evoked by stimulation of the Schaffer collaterals using bipolar electrodes positioned equidistant on both sides of the recording electrode, resulting in two independent stimulation pathways [12]. One stimulation pathway was used for LTP induction by high-frequency stimulation (HFS, 100 Hz, 1 s), while a weak tetanus (35 pulses, 100 Hz) was applied to the second pathway for the induction of the short-term potentiation. Data acquisition and off-line analysis were performed using PClamp9.2 (Axon Instruments).

The trunk blood was collected and serum was extracted via centrifugation (3500 rpm for 10 min at 4 °C) and used for measurement of corticosterone (CORT) concentrations using the Corticosterone ELISA kit RE52211 (IBL International, Hamburg, Germany) according to manufacturer's instructions.

For Western blot, the 2 mm of DH and DH regions of hippocampus (randomized from left/right hemisphere) were manually dissected and homogenized immediately. All preparations were done on ice as described previously [7,19]. Briefly, after semi-dry transfer and blocking, membranes were incubated with primary antibodies for 42 h at 4 °C: rabbit α beta 1 adrenergic receptor (1:1000, Abcam, Cambridge, UK), beta 2 adrenergic receptor (1:200,