Persistent Changes in Ability to Express Long-Term Potentiation/Depression in the Rat Hippocampus After Juvenile/Adult Stress

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Background: The ventral hippocampus (VH) was recently shown to express lower magnitude long-term potentiation (LTP) compared with the dorsal hippocampus (DH). Exposure to acute stress reversed this difference, and VH slices from stressed rats expressed larger LTP than that produced in the DH, which was reduced by stress. Stressful experience in adolescence has been shown to produce long-lasting effects on animal behavior and on ability to express LTP/long-term depression (LTD) of reactivity to afferent stimulation in the adult. We are interested in possible interactions between juvenile and adult stress in their effects of adult plasticity.

Methods: We studied the effects of a composite juvenile (28–30 days) stress, followed by a reminder stressful experience in the young adult (60 days) rat, on the ability to produce LTP and LTD in CA1 region of slices of the VH and DH.

Results: Juvenile or adult stress produced a transient decrease in ability to express LTP in DH and a parallel increase in LTP in VH. Stress in the young adult after juvenile stress produced a striking prolongation of the DH/VH disparity with respect to the ability to express both LTP and LTD into the adulthood of the rat.

Conclusions: These results have important implications for the impact of juvenile stress on adult neuronal plasticity and on the understanding the functions of the different sectors of the hippocampus.

Key Words: Juvenile rat, long-term potentiation (LTP), LTD, slices, stress, ventral hippocampus

The traditional view of the hippocampus as a homogenous structure which is involved in different aspects of memory formation has been replaced recently by a more complex model, which assumes major functional differences between the dorsal and ventral hippocampus (dorsal hippocampus [DH] and ventral hippocampus [VH], respectively). Although the lamellar organization of the hippocampus is maintained along the DH/VH axis, the two sectors are different in afferent and efferent innervation, in distribution of different neurotransmitter and receptors and in functional attributes, as exemplified in lesion and recording studies (1–3). Thus, DH is associated with cognitive functions, spatial and recent memory whereas the VH is associated with affective functions (1–3). Furthermore, this difference is correlated with the ability to generate long-term potentiation (LTP) and depression (LTD) of reactivity to afferent stimulation (4–7). Specifically, LTP in VH is significantly lower than that elicited in the DH.

After an acute stress, LTP in the hippocampus is markedly suppressed either in the DG or in region CA1, in an intact rat or in a slice preparation (8–11). More recent studies have suggested that *N*-methyl-D-aspartate-mediated LTP is suppressed by stress while voltage-gated calcium channel (VDCC) LTP is facilitated (12). With pharmacological tools it has been shown that stress-induced activation of mineralocorticoid receptors (MRs) actually enhances LTP in the dentate gyrus in-vivo, whereas activation of glucocorticoid receptors (GRs) suppresses LTP even to the extent that it is converted to LTD (13). In recent studies we have described a region-specific differential effect of stress on LTP, suppressing it in the DH, as seen by others, but enhancing LTP in the VH (14-16). Thus, a disparity between DH and VH in the effects of stress on plasticity is evident.

Several recent studies have demonstrated long-lasting effects of juvenile stress on adult behavior and brain plasticity (17-19). The juvenile stress varies in type, duration/intensity and age of experience, and the results of exposure to the stressful experience can last throughout life (18). The effects of juvenile stress on adult behavior can be quite striking. Early life (P1) anoxic trauma can affect post-tetanic potentiation 4-8 months later (17), and early life (P9) maternal separation impairs adolescent reinforcement of LTP by a swim stress (19). Even more striking, chronic social stress in 1-month old mice produced cognitive and LTP deficits that were evident even in the aged mice (18).

While juvenile stress has been shown to produce lasting effects on brain and behavior, a more complex issue is can a juvenile stressful experience modulate the reactivity to a stressful experience in the adult? That such an interaction can be highly powerful has been demonstrated in behaving rats (20,21). We therefore set to examine in the present study the combined effects of juvenile and adult exposure to stressful stimuli on the ability to express LTP and LTD in CA1 area of slices of the DH and VH. To this end, we adopted a multiple juvenile stress protocol studied extensively by Richter-Levin *et al.* (22) which produces an effective, long-lasting modification of rat behavior, to find that a reminder stress caused a marked prolongation of the initial effects of juvenile stress on DH/VH disparity with respect to the ability to express LTP.

Methods and Materials

Behavioral Manipulations

All procedures were approved by the local IACUC and adhered to NIH and national regulations. Young (28 days) male Wistar rats were exposed to three stressful experiences, once a day between 9:00 and 11:00 AM, for 3 days. These included a 15 min forced swim in a water bucket (day one), a 30 min stay on an elevated platform

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(day two) and a 2 hours restraint in a narrow tube (day three). At the age of 60 days some rats underwent a 15 min forced swim in a water bucket. These procedures were adopted from Ilin and Richter-Levin (22). We did not study the relative contribution of each stressful experience to the long-lasting effect, as it would require a large number of animals, and instead relied on the earlier studies by Ilin and Richter-Levin (2009). However, it was obvious that these are genuine stressful experiences, studied extensively by us and others, which resulted in acute rise in blood corticosterone (unpublished observations). The combined stressful experience was used to maximize the chance to detect electrophysiological consequences of the stress. At different ages thereafter, the rats were decapitated, their hippocampus removed and sliced.

Electrophysiology

The methods for recording and analysis are detailed elsewhere (7). Briefly, 350 μm slices were cut from rat hippocampus with a McIlwain tissue slicer. Slices were collected from the 2 mm dorsal and ventral poles of the hippocampus, discarding the extreme 350 μm ends. Slices were perfused with ACSF in a standard interface chamber. Recordings were made with a glass pipette containing .75 mol/L NaCl (4 mol/L) placed in the *stratum radiatum* of CA1. Responses were digitized at 5 kHz and stored on a computer. Off-line data analysis was performed with the LTP Program (23) pClamp 8 (Axon Instruments, Union City, California) and Origin software (OriginLab, Northampton, Massachusetts). Excitatory postsynaptic potential (EPSP) slope changes after the LTP induction protocol were calculated with respect to baseline. Each experimental group consisted of six slices taken out from three rats. One rat was used on a day of experiment. Where appropriate, statistical analysis was performed with analysis of variance (ANOVA) followed by post hoc Tukey's comparisons. A three-way ANOVA was conducted in some of the experiments to verify that there were no systematic differences among different rats, and after this analysis the data of the three rats were pooled, and the slices were counted as independent. There were no systematic differences in the magnitudes of the baseline responses in the different conditions.

Results

Initial experiments confirmed the presence of a significant difference in the magnitude of LTP induced in the DH and VH of the 30-day-old rats, by a tetanic stimulation (Figure 1). This marked difference was seen despite lack of difference in basal transmission and input-output relations between the two regions of the hippocampus. At 40 min after a tetanic stimulation, LTP in DH amounted to 1.74 ± .05 of baseline EPSP slope, whereas that of the VH reached 1.24 ± .057 of baseline. This difference was highly significant ($p < .001$). One day, after the three stress sessions in the young animals, LTP in the DH went down to 1.49 ± .05 of baseline, whereas that of the VH went up to 1.82 ± .04 of baseline. Once again, these differences were highly significant (Figure 1).

A procedure to evoke LTD in the slices was used with the second stimulating electrodes on the same slices and involved stimulation at a rate of 1 Hz for 15 min. Measuring EPSP slopes at 20 min after the low-frequency stimulation yielded marked reduction of the EPSP slopes, down to .63 ± .037 in DH and .679 ± .073 of baseline in VH. There was no difference between DH and VH in LTD under these conditions. One day, after stress there was a dramatic disparity between the DH, where the response went further down to .398 ± .04 of baseline, and the VH, where the responses converted from LTD to a slow onset LTP, and reached 1.27 ± .04 of baseline values at 20 min after the low-frequency stimulation (Figure 1, right).

Slices from the same batch of rats were also tested 1 or 3 weeks after the stressful experience (age 5 and 7 weeks) (Figure 1, middle and bottom parts). At these ages the effects of the juvenile stress already dissipated, and no apparent differences were seen between the stressed and the nonstressed control subjects, and the difference between the DH and VH was prominent, so the tetanic stimulation produced a large LTP in the DH and a small one in the VH.

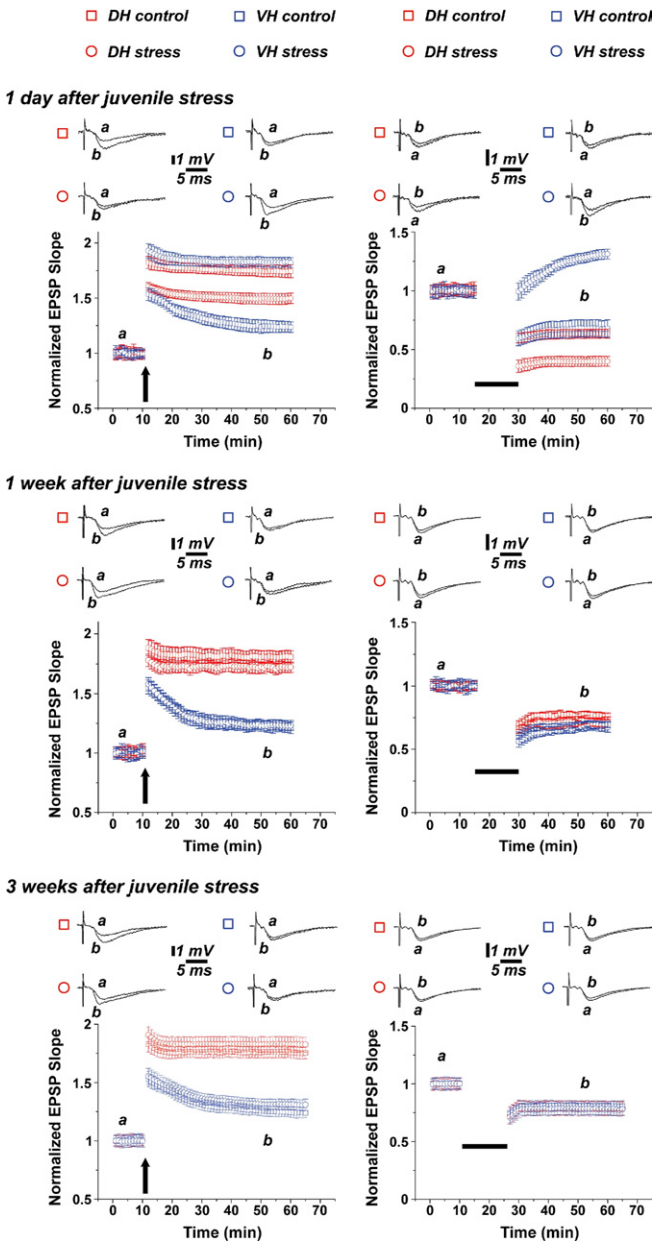

Figure 1. The effects of a combined juvenile stress on long-term potentiation (left columns) and long-term depression (right columns) in the dorsal hippocampus (DH) and ventral hippocampus (VH). The rats were exposed to stressful stimuli at 28, 29, and 30 days of age as detailed. Recording was made on Day 31 (top panels), 1 week after the stress (middle panels), and 3 weeks after the stress (bottom). In each panel of data, the top traces are sample illustrations of original records before *(a)* and 40 min after a tetanic stimulation *(b)*, when analysis was made (Figure 4). Stress affected long-term potentiation and long-term depression in the DH and VH in opposite directions, but this effect was no longer seen 1 week after the juvenile stress and also not seen 2 weeks later (3 week after stress). EPSP, excitatory postsynaptic potential.