Brief Communication

Physiological effects of enriched environment exposure and LTP induction in the hippocampus in vivo do not transfer faithfully to in vitro slices

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A number of experimental paradigms use in vitro brain slices to test for changes in synaptic transmission and plasticity following a behavioral manipulation. For example, a number of previous studies have reported a variety of effects of environmental enrichment (EE) exposure on field potential responses in hippocampal slices, but in no study was it known what changes had been elicited in vivo. In the present study, we recorded from the hippocampus in vivo while rats underwent a brief period of EE. There was no detectable EE-induced change in synaptic efficacy in the dentate gyrus in vivo, but there was an increase in cellular excitability. In slices prepared from the same animals, we failed to observe any evidence of the excitability increase. We next tested whether LTP induction in vivo was better preserved in vitro. However, when slices from these rats were examined, there was no observable change in perforant path synaptic strength, although there was a modest increase in excitability that correlated with the increased excitability observed in vivo. These findings suggest that synaptic changes induced in vivo either are not preserved faithfully or are difficult to detect in hippocampal slices, while changes in cellular excitability are better preserved.

Exposure to an enriched environment (EE) can improve performance on a variety of hippocampus-dependent memory tasks in both normal (Kempermann et al. 1997; Duffy et al. 2001; Teather et al. 2002; Schrijver et al. 2004; Irvine and Abraham 2005) and disease model (Ohlsson and Johansson 1995; Young et al. 1999; Jankowsky et al. 2005; Lazarov et al. 2005; Nithianantharajah and Hannan 2006; Laviola et al. 2008) animals. Previous studies attempting to understand the physiological changes that mediate these effects have yielded mixed results, which may in part be due to the variability in enrichment paradigms used in different laboratories, but which may also be due to the method used to measure hippocampal physiology.

Traditionally, researchers have studied the effects of EE using ex vivo brain slices. Such studies have sometimes reported an increase in synaptic strength following enrichment (Green and Greenough 1986; Foster et al. 1996; Foster and Dumas 2001), but a lack of a change has also been observed (Duffy et al. 2001; Feng et al. 2001; Parsley et al. 2007). The ex vivo approach is predicated on the assumption that EE (or other behavioral) treatment induces changes in neural function that are of sufficient magnitude and extent that they will still be present when the brain is removed and studied in vitro. However, there could be many hidden effects of slice preparation (Kirov et al. 2004) that change or obscure effects occurring in vivo.

In a previous study, we were surprised to find few effects of a 3-mo EE treatment on hippocampal synaptic function and plasticity when assessed in vitro (Eckert et al. 2010), despite our having observed with in vivo recordings substantial effects with shorter periods of EE exposure (Irvine and Abraham 2005; Irvine et al. 2006). We therefore considered the possibility that effects measured electrophysiologically in vivo may not be readily detectable in vitro. Testing this hypothesis requires studying the same animals in vivo and in vitro, a control procedure we are not aware

of having been reported previously in the literature. In the present study, we examined whether the effects of EE or LTP induction in vivo could be detected in hippocampal slices taken from the same animals. We failed to detect any of the in vivo changes, except for a modest increase in cellular excitability following LTP.

Results

Rats with chronically implanted electrodes were exposed to an enriched or social control environment ($n = 4$ each) continuously for 7–15 d. EE exposure caused no detectable change in the medial path fEPSP slope when measured in vivo (Fig. 1A). However, the amplitude of the population spike increased steadily over the course of the first 7 d, reaching an average ($\pm$ SEM) of $49\% \pm 25\%$ ($F_{(3,18)} = 2.7$, $P = 0.07$; Fig. 1B). A more detailed analysis of the fEPSP size using input–output curves taken before and on the last day of EE exposure confirmed the lack of effect on fEPSPs (Fig. 1C), but the population spike was significantly increased at mid- to high-stimulation intensities following enrichment (group $\times$ intensity interaction $F_{(22,66)} = 2.8$, $P < 0.001$; Fig. 1D). Analysis of control rats, which went from individual housing to standard group housing, did not show any change in either the fEPSP or population spike (data not shown).

Following the 7–15 d of differential housing, the same rats used for in vivo recordings were sacrificed and the hippocampi were dissected to test in vitro for effects of enrichment. When preparing slices, care was taken to use slices from the dorsal portion of the hippocampus, where the in vivo recording electrode had been targeted, to ensure that the in vitro measurements were made from approximately the same population of neurons as those recorded in the whole animal. Analysis of the input–output series showed no statistically significant differences between enriched and control fEPSP measures in the medial perforant path (Fig. 1E). Given the lack of any EE effect on the medial path fEPSPs recorded in vivo, this was expected. There was also no significant change in the input–output series for the lateral perforant path (data not shown). Notably, the medial path population

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Figure 1. Effect of a brief period of EE on dentate gyrus in vivo. (A,B) Time course of fEPSP and population spike changes. EE had no effect on the fEPSP slope, but showed a trend toward an increase in the population spike amplitude relative to social controls. *Inset* shows representative waveforms recorded before and after EE (arrowhead). Detailed input–output series from EE animals showed no change in the fEPSP slope (C) following EE, but a significant increase in the population spike amplitude (D). Slices were prepared from the same rats used for in vivo recording. (E) Enriched and control fEPSP slopes were similar. (F) Population spike amplitudes were also similar in EE and social control (SC) animals, despite a significant increase in EE animals in vivo.

spike in EE slices was also not significantly different (indeed, it was slightly reduced) from control slices ($F_{(10,60)} = 1.37$, $P = 0.22$; Fig. 1F), which was unexpected given the increase observed in the intact animal.

Although the in vivo effects of EE on cellular excitability were not observable in vitro, it is possible that the in vivo change was too subtle to be reliably detected in slices from a small group of animals. We therefore changed paradigms, and used a strong high-frequency stimulation (HFS) protocol to induce a robust LTP of both the fEPSP and population spike in vivo in a larger number of animals ($n = 10$). This procedure produced an average increase of $27\% \pm 4\%$ in the fEPSP and $400\% \pm 84\%$ in the population spike ($t_{(9)} = 6.9$ and $t_{(9)} = 4.9$, respectively, both $P < 0.001$; Fig. 2A,B). Input–output curves conducted 1 d before and 1 d after HFS on a subset of five animals showed a significantly increased fEPSP across all but the lowest stimulation intensities, resulting in a significant main effect ($F_{(1,4)} = 96$, $P < 0.001$;

Fig. 2C). The population spike was also significantly increased ($F_{(1,4)} = 44.7$, $P < 0.01$; Fig. 2D).

One day after LTP induction, the animals were sacrificed and slices from both the tetanized and control hemispheres were examined for any LTP-related effects. Despite the reliable fEPSP increase observed in vivo, input–output curves from the medial perforant path did not reveal any differences in fEPSP size between the two hemispheres (Fig. 3A). The lateral perforant path also did not show any change in fEPSP (data not shown). The medial path population spike, however, was larger in slices from the tetanized hemisphere. The average increase across the input–output curve was modest ($28\% \pm 9\%$) compared with the $85\% \pm 10\%$ average increase across the input–output curve observed in vivo, but the increase was consistent across the range of intensities tested ($F_{(1,18)} = 4.8$, $P < 0.05$; Fig. 3B). We predicted that, to the extent that in vivo effects are preserved in vitro, the two measures of LTP-related change should correlate. Indeed, the in vitro measure of percentage spike amplitude increase (tetanized relative to control hemisphere) significantly correlated with the same measure obtained in vivo ($r^2 = 0.42$, $F_{(1,8)} = 5.7$, $P < 0.05$; Fig. 3C).

Discussion

The present data indicate that changes in synaptic transmission and excitability recorded in the hippocampus in vivo, as a result of either environmental enrichment or LTP induction, are not faithfully replicated ex vivo. A number of previous studies have attempted to find changes in hippocampal synaptic transmission following EE using the ex vivo approach, and some have reported an increase in synaptic strength (Green and Greenough 1986; Foster et al. 1996; Foster and Dumas 2001), while others

have reported no change (Duffy et al. 2001; Feng et al. 2001; Parsley et al. 2007). It is possible that some of the variability in the reported effects are due to the different methods of EE exposure used in different laboratories, but the small effects of EE observed in vivo (Irvine and Abraham 2005; Irvine et al. 2006) suggest that EE is perhaps not the ideal behavioral paradigm to study changes in synaptic transmission. Indeed, in another experiment, we attempted to maximize the effect of EE by housing rats in an enriched environment for a minimum of 3 mo and still failed to find any changes in synaptic transmission when recording from slices (Eckert et al. 2010).

A number of studies have demonstrated changes in synaptic strength associated with learning, but relatively few have done so in slices. Cued fear conditioning results in an enhancement of auditory inputs to the lateral amygdala in vivo (Rogan et al. 1997) as well as in vitro (McKernan and Shinnick-Gallagher 1997). Rioult-Pedotti et al. (1998, 2000) showed that learning a

Figure 2. LTP in the dentate gyrus in vivo. Perforant path LTP was induced in 10 rats with a strong HFS protocol, resulting in significant potentiation of the fEPSP (A) and the population spike (B). In a subset of rats ($n = 5$), input–output series were recorded before and 24 h following HFS. Both the fEPSP (C) and population spike (D) were significantly increased following HFS across all but the lowest stimulation intensities.

skilled reaching task strengthened horizontal connections in the primary motor cortex. This effect has also been demonstrated in vivo (Monfils and Teskey 2004; but see Cohen and Castro-Alamancos 2005), and it has been demonstrated both in vivo and in vitro in the same laboratory, although not in the same animals (Hodgson et al. 2005). Moreover, administration of cocaine and methamphetamine in vivo can cause increases in synaptic strength in the ventral tegmental area, as recorded in vitro (Ungless et al. 2001; Saal et al. 2003). In none of these experimental paradigms, however, have the changes reported in vitro been compared with any changes in vivo. Thus, it remains unclear whether the in vitro changes faithfully reflect the intact animal physiology, or whether perhaps the behavioral treatments render the tissue susceptible to changes induced by slice preparation.

In the hippocampus, Lange-Asschenfeldt et al. (2007a,b) found a decrease in CA1 fEPSPs in vitro following learning in a maze task, while Sacchetti et al. (2001) observed an increase in CA1 fEPSPs in vitro following contextual fear conditioning. Using an in vivo preparation, Whitlock et al. (2006) showed a clear increase in CA1 fEPSP size for some excitatory afferents, following learning an inhibitory avoidance task, but it is unlikely these changes would be measurable in vitro given that many afferent synapses showed response depression and the net population effect was no change. Doyère et al. (1995) reported increased dentate gyrus responses in vivo after classical conditioning, and decreased responses after pseudoconditioning. However, in all these experiments, as for the nonhippocampal studies reported above, there was no comparison of in vitro and in vivo recordings made from the same animals.

The process of creating slices offers many opportunities for disrupting the natural state of the brain tissue, and a number of factors may be responsible for the disruption of the in vivo synaptic state. Previous studies have shown that LTP can be reversed by

subsequent afferent stimulation (Staubli and Lynch 1990; Staubli and Chun 1996; Abraham and Huggett 1997), brief hypoxia (Arai et al. 1990b), rapid cooling and rewarming of tissue (Bittar and Muller 1993), and release of adenosine (Arai et al. 1990a). Any or all of these effects may have occurred during slice preparation and contributed to the reversal of LTP induced in vivo. Counter to this hypothesis, however, is the fact that most treatments affecting reversal of LTP are generally effective only during a relatively brief period following LTP induction (on the order of minutes), although LTP reversal at long intervals has also been reported for the dentate gyrus in vivo (Abraham et al. 2002). In the present experiment, we waited 24 h following LTP induction before preparing slices to allow the potentiation to stabilize, but we still cannot discount the possibility that some neurotransmitter or neuromodulator released during slice preparation reversed the in vivo LTP. Another possible reason for the lack of observable LTP ex vivo is the dramatic structural changes that occur at the dendritic level during slice preparation. Kirov et al. (2004) demonstrated that dendritic spines disappear when a slice is chilled and then reappear upon rewarming, and even overproliferate.

Even if the reappearance of spines upon rewarming manages to re-establish the synaptic strengths in vivo, any overproliferation of spines could change synaptic transmission measures at a population level, assuming the new spines are functional. Kirov et al. (2004) found that these marked changes were avoided if the sodium chloride in the ACSF was replaced with sucrose. In the present study, we used sucrose-ACSF for the dissection, and even perfused the animals with sucrose ACSF prior to decapitation in an effort to preserve the in vivo state as closely as possible. This suggests that, even without the spine alterations, the in vivo synaptic transmission state is difficult to reproduce in vitro.

LTP induction typically involves both synaptic potentiation and an increase in cellular excitability, termed EPSP-spike (E-S) potentiation. Different mechanisms have been proposed for E-S potentiation, including a change in the balance of synaptic excitation and inhibition (Abraham et al. 1987), a change in the intrinsic excitability of the cells (Xu et al. 2005), or a combination of the two (Daoudal et al. 2002). After LTP induction in vivo, we observed increased excitability in vitro even though synaptic potentiation did not survive the slice preparation procedure. Changes in cellular excitability have also been observed ex vivo following different learning tasks, such as trace eye-blink conditioning (Moyer et al. 1996; Thompson et al. 1996) and contextual fear conditioning (McKay et al. 2009). Similar changes in excitability also occur in the piriform cortex following olfactory discrimination learning (Saar et al. 1998). While it is not clear that the mechanism of increased excitability is similar across these studies, they suggest, together with our observation of increased excitability in vitro following LTP induction in vivo, that excitability changes are more readily maintained and detected ex vivo than changes in synaptic strength. Overall, we conclude that measures of synaptic strength in vitro do not necessarily

Figure 3. Is in vivo LTP observable in vitro? Slices were prepared 24 h following LTP induction, and input–output series were recorded from the tetanized and control hemispheres. (A) There was no observable increase in the medial perforant path fEPSP slope. (B) The population spike was significantly larger in the tetanized hemisphere compared with the control hemisphere. *Inset* shows representative waveforms from tetanized (arrowhead) and control slices from the same animal. (C) There was a significant correlation between the in vivo population spike LTP and the in vitro population spike amplitude, measured as a ratio of the tetanized to control spike amplitude.

reflect the in vivo state accurately, and therefore measures made using only the ex vivo approach should be interpreted cautiously.

Materials and Methods

All experiments were carried out with approval of the University of Otago Animal Ethics Committee, and in accordance with all New Zealand animal welfare legislation.

Adult male Sprague-Dawley rats (350–500 g) were implanted with electrodes in the medial perforant path and dentate gyrus using previously described procedures (Abraham et al. 2002). EE rats were implanted unilaterally, and LTP rats were implanted bilaterally. Baseline recording began 10 d following surgery, and continued three times per week until the response was stable for

at least 1 wk. Once the response was stable, an input–output series was recorded using a range of stimulus currents (10–500 μA), and the following day the treatment condition began (either enriched environment or LTP induction).

For the enriched environment experiment, rats were randomly assigned to one of two housing conditions: enriched environment (EE) or social control (SC). For the enriched environment, two to four rats were housed continuously in a large fiberglass box (80 × 80 × 80 cm) that contained a three-dimensional arrangement of objects such as tunnels, ladders, boxes, and plastic toys. The objects were changed weekly to ensure continued novelty and complexity. SC animals lived in groups of two to four in a standard plastic group cage (50 × 35 × 25 cm) that contained only bedding. Baseline recordings were made on days 1, 4, and 7 of EE treatment and in vitro recordings began on day 8. On the day prior to in vitro recording, a pair of animals was selected, one EE and one SC, and an input–output series was recorded from both. Over the next 2 d, these animals were used for in vitro recording, and the animal used on a particular day was selected randomly by another member of the laboratory so that the experimenter was blind to the treatment condition. This process was repeated until all of the animals were used. Thus, the total time spent in the enriched environment varied from 7 to 15 d, but the final input–output series was always recorded 1–2 d prior to in vitro recording.

LTP was induced with a strong high-frequency stimulation (HFS) protocol that results in a robust, stable LTP in the dentate gyrus (Abraham et al. 2002). To ensure that the potentiation was lasting, the rat was returned to its home cage for 1 d and recordings were made again prior to sacrifice for the in vitro experiments. Input–output series were recorded before and 24 h following LTP induction.

For in vitro electrophysiology, the animal was taken directly from its experimental housing and deeply anesthetized with ketamine (100 mg/kg, i.p.). Before decapitation, the animal was perfused with a cold sucrose-containing artificial cerebrospinal fluid (ACSF; composition: 210 mM sucrose, 3.2 mM KCl, 1.25 mM NaH_2PO_4 , 26 mM NaHCO_3 , 2.5 mM CaCl_2 , 1.3 mM MgCl_2 , and 10 mM D-glucose) of the same composition as described below for recordings, except that sucrose is substituted for sodium chloride. This is a solution commonly used during cutting procedures in other experiments and helped preserve slice health during removal of the headcap during the dissection procedure. Transverse hippocampal slices (400 μm) were cut from the dorsal end of the hippocampus (where the chronic recordings were made) so that in vitro measures were made in approximately the same location as the in vivo recording. As evidence of this, in 10 out of 10 tetanized hemispheres, the electrode tract made by the chronic recording electrode was visible in at least one slice. Following cutting, slices were maintained in a submerged recording chamber perfused with oxygenated ACSF (composition: 124 mM NaCl, 3.2 mM KCl, 1.25 mM NaH_2PO_4 , 26 mM NaHCO_3 , 2.5 mM CaCl_2 , 1.3 mM MgCl_2 , and 10 mM D-glucose) maintained at 32.5°C. Slices were allowed to equilibrate for at least 1.5 h before testing began. Importantly, the experimenter was blind to treatment conditions until completion of the experiments.

Three slices from each hemisphere were used for recording, and the data from the best two slices in each hemisphere (the ones with the largest fEPSP) were averaged together to yield a single measure for that hemisphere. In the enriched environment experiment, the data from the two hemispheres were then averaged to yield a single measure per animal. fEPSPs were evoked by stimulation with a tungsten wire and recorded with a glass pipette filled with 2 M NaCl (1–2 MΩ). Input–output curves were performed using an increasing series of stimulation intensities (range 10–250 μA). Recordings were made simultaneously in the dendritic and cell body layers, and measurements were made of the initial slope of the fEPSP and the height of the population spike. At each intensity, three responses were averaged for analysis purposes. The lateral and medial perforant paths were studied separately by adjusting the position of the stimulating electrode. Paired-pulse facilitation and inhibition were used to confirm stimulation of the lateral and medial perforant paths, respectively.

Input–output series from in vivo recordings were normalized prior to analysis by expressing them as a percentage of the response evoked by the maximum stimulation intensity prior to enrichment or LTP. Significant differences on input–output curves were determined by repeated measures ANOVA. LTP induction was statistically analyzed using a one-sample *t*-test.

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