The α5GABA$_A$ Receptor Modulates the Induction of Long-Term Potentiation at Ventral But Not Dorsal CA1 Hippocampal Synapses

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ABSTRACT The hippocampal synapses display conspicuous ability for long-term plasticity which is thought to underlie learning and memory. Growing evidence shows that this ability differs along the long axis of the hippocampus, with the ventral CA1 hippocampal synapses displaying remarkably lower ability for long-term potentiation (LTP) compared with their dorsal counterpart when activated with high-frequency stimulation. Here, we show that low frequency, 10 Hz stimulation induced LTP more reliably in dorsal than in ventral CA1 field. Blockade of alpha5 subunit-containing GABA$_A$ receptors eliminated the difference between dorsal and ventral hippocampus. We propose that α5GABA$_A$ receptor-mediated activity plays a crucial role in regulating the threshold for induction of LTP especially at the ventral CA1 hippocampal synapses. This might have important implications for the functional specialization along the hippocampus. **Synapse 00:000–000, 2014.** © 2014 Wiley Periodicals, Inc.

INTRODUCTION

The hippocampus is importantly involved in learning and memory (Eichenbaum, 2004). A large body of data suggests that the involvement of the hippocampus to the different functions appears to be segregated along the septo-temporal or dorso-ventral axis of the structure (Fanselow and Dong, 2010; Small, 2002), in part attributed to the distinct connections of the different hippocampal segments to other brain structures (Petrovich et al., 2001; Risold and Swanson, 1996). In addition, an emergent body of evidence suggests that the intrinsic local circuit of the hippocampus displays specializations in its functional organization between its dorsal (DH) and ventral (VH) poles. A particularly notable difference between DH and VH have been found on the capability for induction of a classical form of NMDA receptor-dependent long-term potentiation (LTP) by high-frequency stimulation which is remarkably lower in VH than DH CA1 synapses (Colgin et al., 2004; Maggio and Segal, 2007; Maruki et al., 2001; Papatheodoropoulos and Kostopoulos, 2000a). However, the mechanisms underlying this difference remain unclear. Long-term synaptic plasticity is thought to be a fundamental mechanism underlying learning and memory (Morris, 2003); therefore differences in the ability for LTP might have important implications for learning and memory.

It is known that at the hippocampal synapses the induction of LTP that depends on the activity of NMDA receptors is strongly facilitated by lowered synaptic GABAergic inhibition (Chapman et al., 1998; Wigstrom and Gustafsson, 1983). One of the predominant GABA$_A$ receptor subtypes in the CA1 field contains the α5 subunit (Pirker et al., 2000; Sur et al., 1999) contributing mainly to extrasynaptic or tonic (Caraiscos et al., 2004) and secondarily to synaptic or phasic (Vargas-Caballero et al., 2010) inhibition. The ventral CA1 field expresses higher levels of α5 subunit as compared with its dorsal counterpart (Sotiriou et al., 2005). Also, the levels of extracellular GABA are higher in the CA1 field of the ventral compared with the dorsal hippocampus (Hortnagl et al., 1991). Relatively elevated extracellular GABA levels

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are required for $\alpha5GABA_ARs$ to contribute to the tonic activity (Scimemi et al., 2005). Reduction in the $\alpha5GABA_AR$-mediated transmission facilitates LTP in the hippocampus (Atack et al., 2006). Importantly, this facilitation was observed when low-frequency (10 Hz) but not high-frequency (100 Hz) stimulation was used for induction of LTP (Martin et al., 2010). We hypothesized that 10 Hz stimulation will induce less effectively LTP in VH because of the higher $\alpha5GABA_AR$-mediated activity in VH and that pharmacological blockade of $\alpha5GABA_AR$ will assist the induction of LTP more in VH than DH.

METHODS

Thirty-three Wistar male rats 1–3-month old were used. All animal treatment and experimental procedures were conducted in accordance with the Directive Guidelines for the care and use of Laboratory animals of the European Communities Council (European Communities Council Directive Guidelines 86/609/EEC, JL 358, 1, December 12, 1987) and they were approved by the local ethical committee. All efforts were made to minimize animal suffering and to reduce the number of animals used. Transverse slices 500–550-μm thick were sectioned from the region extending more than 1 and less than 3.5 mm from the dorsal and the ventral ends of the hippocampus using a McIlwain tissue chopper. To maintain an orthogonal cut plane during sectioning of the two poles a turn of the plate supporting the structure was used. In each experiment (i.e., animal) one to two slices from each pole were selected for experimentation. Slices were immediately transferred to the recording chamber, maintained at a temperature of $31.5 \pm 0.5°C$, perfused with standard medium containing (mM): NaCl 124, KCl 4, $MgSO_4$ 2, $CaCl_2$ 2, NaH_2PO_4 1.25, $NaHCO_3$ 26, and glucose 10, at a pH 7.4. Slices were continuously humidified with 95% O_2 and 5% CO_2 gas mixture. Recordings were made from the stratum radiatum and stratum pyramidale of CA1 field using carbon fiber electrodes (7 μm). Field potentials consisting of afferent fiber volley (Fv, i.e., the population action potential of the presynaptic axons), excitatory postsynaptic potentials (EPSP), and population spikes (PS) were evoked using a bipolar platinum/iridium electrode (25 μm) placed at Schaffer collaterals and electrical pulses (100 μs) were delivered every 30 s. EPSP was quantified by its rising slope while Fv and PS were quantified by their amplitude. From the input/output curves we measured the current intensity as well as the EPSP that produced a half-maximum PS (I_{50}, $EPSP_{50}$, respectively). For the induction of LTP, 900 pulses at 10 Hz were delivered at the baseline stimulation strength that produced a near threshold EPSP ($EPSP_{thr}$). The inverse agonist for the benzodiazepine site of $\alpha5GABA_ARs$, 11,12,13,13a-Tetrahydro-7-methoxy-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylic acid, ethyl ester (L-655,708, 100 nM; Tocris Cookson, UK) (Chambers et al., 2003; Quirk et al., 1996) was used at 100 nM. Though the concentration of 100 nM might be on the limits of the drug selectivity for $\alpha5GABA_ARs$ (Vargas-Caballero et al., 2010) there is some evidence suggesting the absence of non-specific (e.g., synaptic) drug effects at this concentration, including the absence of any sign of even subtle reduction in synaptic inhibition and the significant enhancement in the amplitude of sharp wave-ripples (Papatheodoropoulos and Koniaris, 2011), an activity particularly sensitive to changes in synaptic $GABA_AR$-mediated transmission. In addition, L-655,708 at the very high concentration of 5 μM that blocks tonic current in pyramidal neurons leaves synaptic currents unaffected (Yamada et al., 2007). L-655,708 was first prepared as stock solution in Dimethyl-sulfoxide (DMSO); then it was dissolved in the perfusion medium which contained a final volume of DMSO lower than 0.005%. Signals were amplified, filtered at 0.5 Hz–2 kHz, digitized at 4–5 kHz, and stored for off-line analysis.

Each animal contributed to each experimental condition with a single slice from each hippocampal pole. Thus, throughout the text "*n*" indicates the number of animals included in the analysis. The values of the various parameters are expressed as mean ± s.e.m. The independent *t*-test and the paired *t*-test, as well as the non parametric Mann–Whitney *U* test and the Wilcoxon test were used for comparisons between two groups of values. For the comparisons between multiple groups of data Mixed Models Analysis (MMA) was used, due to the presence of missing data. Multiple comparisons were performed in a case by case setting. The percentage change of EPSP/Fv was set as the response variable. The explanatory variables, Locus (dorsal, ventral) and Condition were treated as fixed effects variables, whereas the Intensity was treated as a repeated measure for random effects as well as for fixed effects (since a single intensity was used repeatedly on an uneven scale). Several stepwise post hoc tests were performed whenever appropriate.

RESULTS

The diagrams in Figure 1A–1E show the input/output relationships between the stimulation strength or presynaptic activation and the presynaptic or postsynaptic response, while the collective data are shown in Table I. The EPSP increased nearly linearly with increasing stimulation strength (Fig. 1A). This relationship was statistically similar between DH and VH; nevertheless at increasing stimulation strengths the EPSP tended to acquire greater values in the ventral than in the dorsal slices. A similar quasi-linear relationship was also observed between the stimulation strength and the amount of the

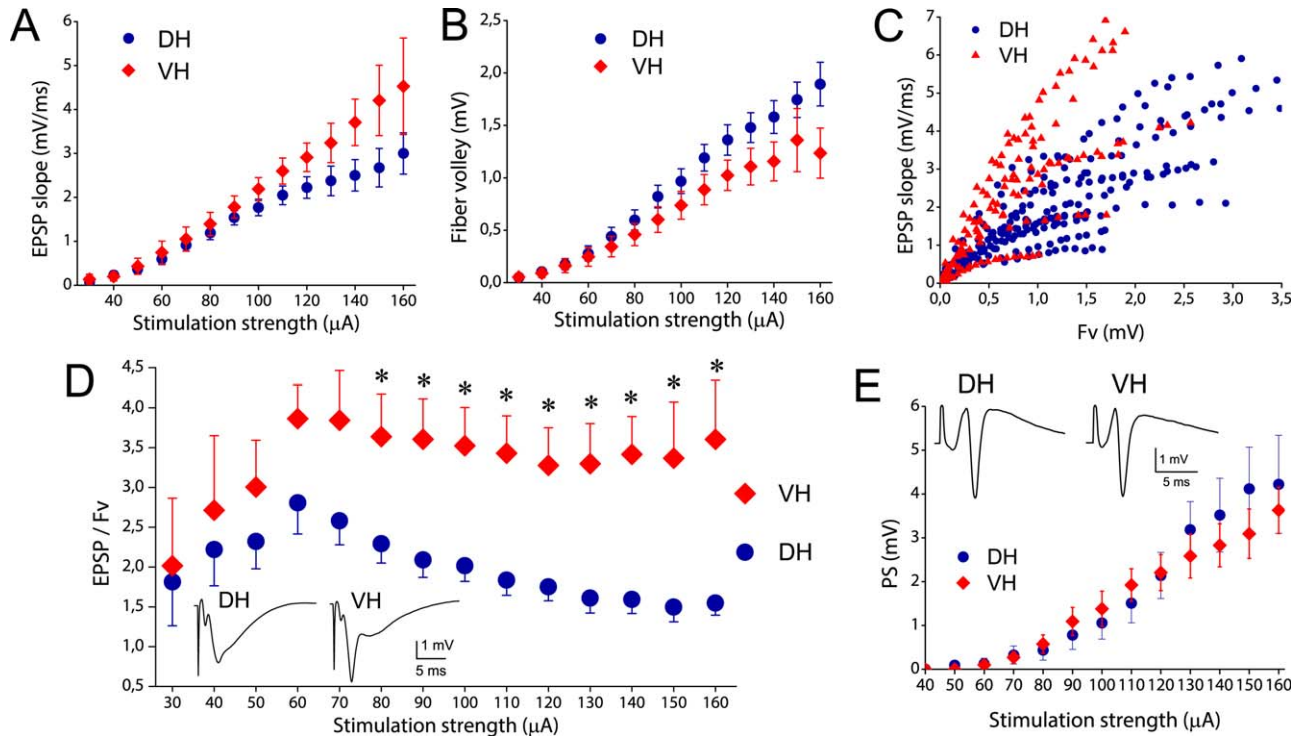

Fig. 1. Higher synaptic effectiveness of VH compared with DH. **A**: Input/output curves between stimulation strength and postsynaptic activation (EPSP) showing no significant difference between DH and VH. **B**: Input/output curves between stimulation strength and presynaptic excitation (Fv) showing no significant difference between DH and VH. **C**: Scatter plot of the relationship between presynaptic excitation (Fv) and postsynaptic activation (EPSP). **D**: Input/output curves between stimulation strength and synaptic effectiveness (EPSP/Fv) showing that at moderate and higher levels of presynaptic stimulation, VH had a significantly greater synaptic effectiveness than DH. Asterisks denote statistical significance at $P < 0.001$. Insert shows examples of evoked responses. Note that in VH was produced greater EPSP with smaller Fv. **E**: Input/output curves between stimulation strength and principal cell firing (PS). Examples of PSs evoked by a stimulation of 120 μA are given in the insert. Data in this figure shown as mean ± s.e.m. were obtained from 19 dorsal and 16 ventral slices taken from 19 animals. For clarity purposes data shown in C were obtained from a random subset of nine dorsal and nine ventral slices taken from nine animals.

presynaptic activation represented by the fiber volley (Fig. 1B). Again, no statistically significant differences between DH and VH were observed, yet as the stimulation strength increases the Fv tends to acquire smaller values in the ventral compared with dorsal slices. Consequently, at similar levels of presynaptic activation, defined by Fv, the EPSP was greater in ventral slices (Fig. 1C). Because the size of Fv indicates the number of activated afferent fibers (Andersen et al., 1978), Fv is a very reliable index of presynaptic activation (Andersen et al., 1980) and estimates of synaptic effectiveness that take into account the Fv are particularly accurate. This should be even more crucial when comparing synaptic responses and estimating synaptic effectiveness between different slices or animals, where the variability in the number of afferent fibers activated by a given amount of electrical stimulation from experiment to experiment may differ considerably. Therefore, in quantifying synaptic effectiveness and making comparisons between slices from DH and VH we used the ratio EPSP/Fv. Plotting EPSP/Fv against stimulation intensity results in a curve which is not expected to significantly change with changes in the stimulation strength (Fig. 1D) since both components in the ratio, EPSP and Fv, change rather linearly with the stimulation strength (Fig. 1A and 1B) (Andersen et al., 1978). Indeed, in the ventral hippocampus the values of EPSP/Fv were statistically similar between the different levels of stimulation. However, in the dorsal hippocampus, at stimulation strengths (>70 μA) that produced EPSPs of more than 1 mV and suprathreshold stimulation strengths that induced PS, the EPSP/Fv ratio declined gradually along with increasing levels of stimulation (ANOVA, $F(36,172) = 3.73$, $P < 0.0005$). Most importantly, at these levels of activation the ratio EPSP/Fv was significantly greater in VH than in DH (MMA, *t*-test $P < 0.000$, *F*-test $F(1,247) = 101.205$, $P < 0.005$, Fig. 1D). In addition to synaptic effectiveness, we made comparisons between DH and VH for the indexes of neuronal and postsynaptic excitability (Table I, Fig. 1E). None of those indexes that quantify neuronal (PS_{th}, I_{50}) and postsynaptic ($EPSP_{50}$, PS/EPSP) excitability significantly differ between the two hippocampal poles.

TABLE I. Comparison of the various measures of field potentials between dorsal (DH) and ventral (VH) hippocampal slices

	$EPSP_{half}$ (mV/ms)	$EPSP_{half}$/Fv	$EPSP_{max}$ (mV/ms)	$EPSP_{max}$/Fv	PS_{th} (mV)	I_{50} (μA)	PS_{max} (mV)	$EPSP_{50}$ (mV/ms)	PS/EPSP
DH	1.65 ± 0.22 (20)	2.35 ± 0.18 (20)	3.31 ± 0.48 (20)	1.53 ± 0.16 (20)	0.78 ± 0.33 (12) $I = 90$ μA	116.94 ± 13.17 (12)	5.14 ± 0.83 (14)	3.13 ± 0.30 (12)	0.94 ± 0.08 (11)
VH	2.42 ± 0.36 (15)	4.43 ± 0.42* (15)	4.86 ± 0.76 (15)	2.89 ± 0.3* (15)	0.58 ± 0.21 (7) $I = 80$ μA	90.21 ± 9.69 (10)	4.73 ± 0.79 (10)	3.51 ± 0.40 (10)	0.72 ± 0.11 (10)

Values into parenthesis represent the number of animals included in statistics.
Asterisks indicate statistically significant differences between DH and VH at $P < 0.001$ (Mann–Whitney U test and independent t-test).

Figure 2 shows the input/output curves for EPSP/Fv constructed before and 60 min following 10 Hz-stimulation, in standard conditions (naive slices) and under perfusion with the inverse agonist of $GABA_A$ receptors 100 nM L-655,708. DH slices either naive or under L-655,708 displayed LTP at almost every activation strength. On the contrary, LTP was more effectively induced in VH slices perfused with L-655,708 than in naive VH slices. The results of LTP that was induced in naive slices at a stimulation intensity that produced $EPSP_{thr}$ are shown in Figure 3 (bottom-left insert). Immediately after the 10 Hz stimulation, the synaptic response was depressed in both DH and VH. This depression lasted for 5–6 min and it was followed by a gradual increase in the EPSP/Fv which potentiated and reached maximal values at 20–30 min. The percentage of potentiation observed at 60 min after the induction was similar between DH ($17.7 \pm 0.19\%$, $n = 9$) and VH ($16.84 \pm 0.31\%$, $n = 9$). However, when we compared the potentiation at higher stimulation levels we observed significant differences between DH and VH (Fig. 3A). Thus, while DH displayed significant potentiation at all levels of synaptic activation leading to suprathreshold EPSPs (>60 μA, one-sample $t(18) = 5.91$, $P < 0.005$), significant potentiation in VH occurred in a much less consistent pattern. Thus, the magnitude of LTP in DH ranged from $23.5 \pm 5.3\%$ to $33.6 \pm 6.4\%$ whereas the magnitude of LTP in the VH was considerably lower and ranged between a minimum of $0.5 \pm 4.3\%$ and a maximum of $20.1 \pm 7.2\%$. As a result, at the range of suprathreshold stimulations the magnitude of LTP was significantly greater in DH ($28.8 \pm 1.8\%$, $n = 19$) than in VH ($9.9 \pm 1.5\%$, $n = 16$), (MMA, t-test $P < 0.000$, F-test $F(1,109) = 21.197$ $P < 0.000$, Fig. 3A). When taking into account the entire range of activation levels (from 50 to 170 μA), including subthreshold ones, the mean amplitude of LTP was again significantly greater in DH ($30.2 \pm 2.0\%$, $n = 19$) than in VH ($13.5 \pm 2.2\%$, $n = 16$), (MMA, t-test $P < 0.000$, F-test $F(1,113) = 18.547$ $P < 0.000$).

Figure 3B shows the results on LTP induced in the presence of the inverse agonist of $\alpha 5GABA_A$Rs L-655,708, which was added 30 min before the delivery of 10 Hz stimulation and was applied for the entire duration of the experiment. Under these conditions LTP of similar amplitude was developed in DH and VH. In particular, LTP ranged from 6.5% to 30.3% (mean $22.4 \pm 2.3\%$) in DH ($n = 20$) and from 7.2% to 26.8% (mean $20.3 \pm 2.0\%$) in VH (MMA, t-test $P > 0.1$, F-test $F(1,106) = 0.044$ $P > 0.1$, $n = 17$). The similarity in the magnitude of potentiation between DH and VH was observed at all levels of synaptic activation. Whereas DH did not exhibit any significant change in the LTP levels, VH long-term potentiation was significantly

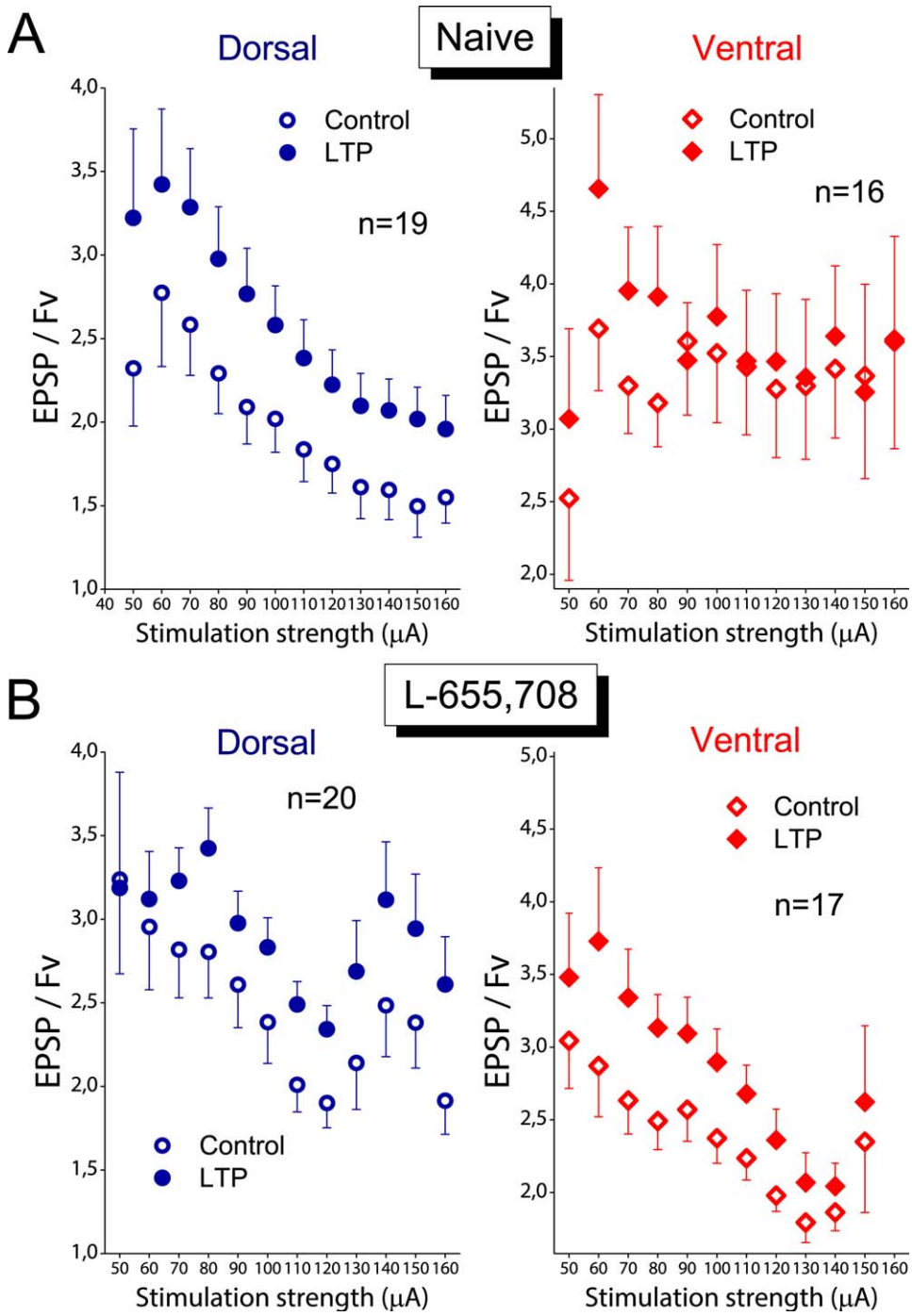

Fig. 2. Input/Output curves of EPSP/Fv obtained from DH and VH naïve slices (**A**) and DH and VH slices perfused with L-655,708 (**B**). Recordings made before (open symbols) and 60 min after the delivery of 10 Hz stimulation (filled symbols) show that L-655,708 facilitated the induction of LTP in ventral slices only. All comparisons were made using paired *t*-tests and MMA. Dorsal Naive, control mean = 2.01 ± 0.14, LTP mean = 2.5 ± 0.14, paired $t(214) = -12.62$, $P < 0.000$, *F*-test $F(1,169) = 189.906$ $P < 0.000$, $n = 19$. Ventral Naive, control mean = 3.54 ± 0.3, LTP mean = 3.91 ± 0.3, paired $t(147) = -4.93$, $P < 0.000$, *F*-test $F(1,81) = 41.573$ $P < 0.000$, $n = 16$. Dorsal Drug, control mean = 2.82 ± 0.23, LTP mean = 3.28 ± 0.22, paired $t(198) = -4.18$, $P < 0.000$, *F*-test $F(1,160) = 138.141$ $P < 0.000$, $n = 17$. Ventral Drug, control mean = 2.69 ± 0.19, LTP mean = 3.26 ± 0.2, paired $t(153) = -9.15$, $P < 0.000$, *F*-test $F(1,135) = 66.107$ $P < 0.000$, $n = 17$. "*n*" indicates the number of animals used.

higher under L-655–708 perfusion, than in naive conditions (MMA, *t*-test $P < 0.05$, *F*-test $F(1,95) = 3.460$ $P < 0.05$).

The comparisons in LTP presented in Figure 4, made at the stimulation intensity that produced half-maximum EPSP/Fv, indicate that L-655,708

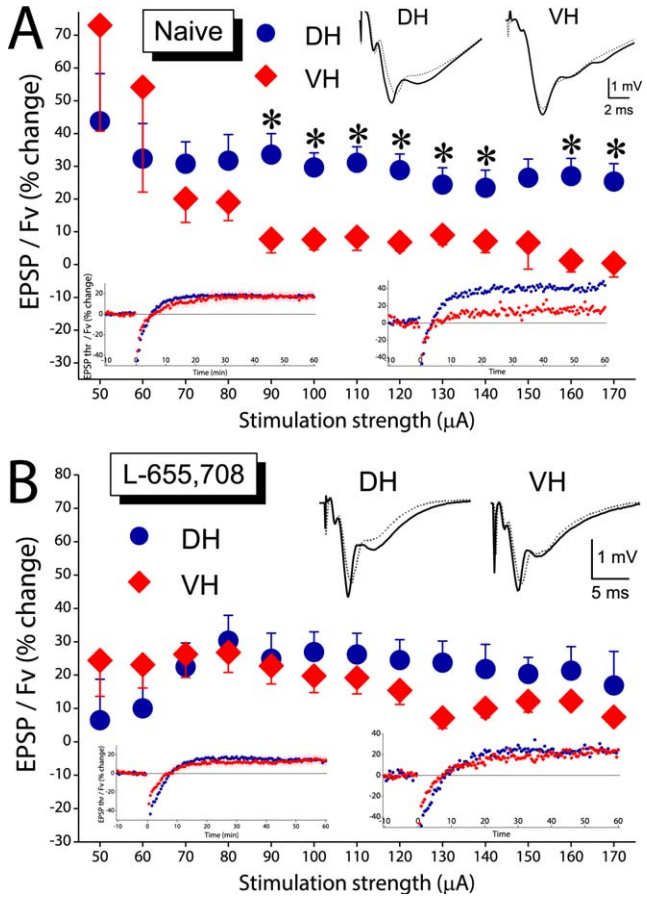

Fig. 3. VH exhibits a lower ability for a 10 Hz-induced LTP, which was reversed by a blockade of $\alpha5GABA_A$Rs. **A**: Graph showing the relationship between LTP of EPSP/Fv and levels of afferent activation as determined by input/output curves constructed before and 60 min after the delivery of 10 Hz stimulation. Asterisks denote statistically significant differences between DH (19 animals) and VH (16 animals). See text for details about statistical analysis. Note that statistically significant differences between DH and VH were found at stimulation intensities suprathreshold for principal cell firing. **B**: Input/output relationship between LTP of EPSP/Fv and stimulation strength. Note that blockade of $\alpha5GABA_A$Rs by L-655–708 (100 nM) increased the ability for LTP in the VH (17 animals) but not in the DH (20 animals) (compare "B" with "A"). Examples of EPSP/Fv waveforms before (dot lines) and 60 min after the delivery of 10 Hz stimulation (solid traces) are shown in the top-right inserts (in A and B). The time course plots of percentage change at near threshold stimulation intensities ($EPSP_{thr}$) in absence and presence of L-655,708 are shown in the two bottom-left inserts, in A and B, respectively. Note that at this stimulation level no significant differences between DH and VH were observed. In the bottom-right inserts examples of LTP induced at stimulation strengths that evoked half-maximum EPSP ($EPSP_{half}$) in DH and VH naïve and drug-perfused slices are shown.

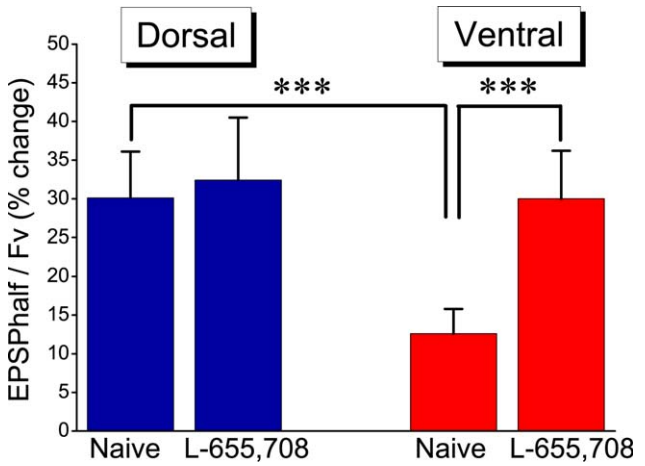

Fig. 4. Blockade of $\alpha5GABA_A$Rs enhanced the ability for LTP of EPSP/Fv only in VH. Collective data of the percent change in $EPSP_{half}$/Fv in DH and VH observed 60 min after the 10 Hz stimulation in naive slices (19 dorsal, mean = 30.14 ± 6, 16 ventral, mean = 12.61 ± 3.2) and slices perfused with the inverse agonist of $\alpha5GABA_A$Rs L-655,708 (20 dorsal, mean = 32.35 ± 8.1, 17 ventral, mean = 29.95 ± 6.2). $EPSP_{half}$ indicates the half-maximum EPSP slope observed in each slice. Asterisks denote statistically significant differences (Mann–Whitney U test and independent t-test; comparison between DH and VH, paired $t(33) = 2.34$, $P < 0.001$; comparison between the two groups of VH slices, paired $t(31) = -2.41$, $P < 0.001$).

significantly enhanced the magnitude of LTP in the ventral hippocampus only.

DISCUSSION

In this study, we demonstrated that: (a) the CA1 synapses display greater efficacy in VH than in DH, (b) 10 Hz stimulation induces LTP less reliably in VH than in DH, and (c) the dorsal-ventral difference in LTP was eliminated after blockade of $\alpha5GABA_A$Rs. In agreement with previous reports (Maggio and Segal, 2007; Papatheodoropoulos and Kostopoulos, 2000a) we found similar EPSPs in DH and VH. However, examining the ratio EPSP/Fv, we found that the synapses of VH displayed considerably higher effectiveness than their DH counterparts. This difference could be attributed to several mechanisms, including the number of active synaptic contacts per axon, the resistance of the dendritic membrane, the amount of neurotransmitter release and the fast GABAergic inhibition. There is no available comparative data between DH and VH on the number of synapses between Schaffer collaterals and CA1 pyramidal cells. The recently demonstrated higher input resistance of the apical dendrites in VH compared with DH cells (Dougherty et al., 2012) could explain the higher EPSP/Fv ratio in VH. A longer mean distance between adjacent synapses in VH leading to more effective spatial summation of postsynaptic potentials might be an alternative explanation for the higher EPSP/Fv ratio in VH. This would also explain the decline in EPSP/Fv ratio with increasing stimulation strength observed in DH only; that is, assuming that synapses are randomly recruited with increasing stimulation strength then the mean distance of the activated synapses will decrease progressively with increasing stimulation leading to reduced spatial summation of postsynaptic potentials due to shunting effects of neighboring synapses. Yet another

explanation for the higher EPSP/Fv ratio in VH might be the probability of transmitter release. Taking into account that the ventral CA1 synapses display characteristic low paired-pulse facilitation when compared with the dorsal ones (Maruki et al., 2001; Papatheodoropoulos and Kostopoulos, 2000b) and that facilitation is inversely correlated with release probability (Zucker and Regehr, 2002) we propose that a relatively higher basal level of release probability may contribute to the higher synaptic effectiveness in VH. A lower GABAergic synaptic inhibition may also contribute to the higher EPSP/Fv in VH. Indeed, VH has a lower synaptic GABAergic inhibition as compared with DH (Papatheodoropoulos et al., 2002; Petrides et al., 2007).

In keeping with previous reports (Wang and Wagner, 1999) we found that 10 Hz stimulation induced LTP in the CA1 field of DH. Previous reports have shown that VH has a remarkably lower ability for NMDAR-dependent LTP induced by high-frequency stimulation (100 Hz, 1 s) (Maggio and Segal, 2007; Maruki et al., 2001; Papatheodoropoulos and Kostopoulos, 2000a). This study shows that also the lower frequency of 10 Hz that induces NMDAR-dependent LTP (Martin et al., 2010) is significantly less effective in inducing LTP in VH compared with DH.

One of the main mechanisms controlling the induction of LTP is GABAergic transmission (Davies et al., 1991; Wigstrom and Gustafsson, 1983), which consists of synaptic and extrasynaptic components (Lindquist and Birnir, 2006; Mody, 2001). The subtype of $GABA_A$Rs that contains the α5 subunit is one of the most abundant in CA1 (Sur et al., 1999) participating in tonic (Caraiscos et al., 2004) as well as phasic transmission (Vargas-Caballero et al., 2010) and blockade of α5$GABA_A$R-mediated transmission facilitates the induction of LTP following 10 Hz stimulation (Martin et al., 2010). The location of α5$GABA_A$Rs at the base of dendritic spines makes them ideal modulators of NMDAR-mediated activity (Crestani et al., 2002). Consequently, the preferential facilitation of 10 Hz-induced LTP in VH following blockade of α5$GABA_A$Rs might indicate a higher involvement of these receptors in the regulation of synaptic plasticity in VH compared with DH. This is the first evidence showing that α5$GABA_A$Rs play a different role between DH and VH.

An emerging idea from the comparative studies between DH and VH at the behavioral level is the different involvement of the two poles to distinct types of memory. Accordingly, while DH plays a prominent role in the spatial memory (Colombo et al., 1998; Maguire et al., 2000) VH has a more important participation in fear extinction memory (Orsini et al., 2011; Sierra-Mercado et al., 2011), a type of memory in which α5$GABA_A$Rs are significantly involved (Yee et al., 2004). Considering that long-term plasticity is thought to underlie learning and memory, the different modulation that α5$GABA_A$R plays on LTP between DH and VH is consistent with the abovementioned observations and it may represent a mechanism that contributes to the preferential implication of the ventral hippocampus to fear extinction memory.

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