# HIPPOCAMPAL CA1 SYNAPTIC PLASTICITY AS A GAMMA TRANSFER FUNCTION

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**Abstract**—The capacity of activity-dependent synaptic modification is essential in processing and storing information, yet little is known about how synaptic plasticity alters the input–output conversion efficiency at the synapses. In the adult mouse hippocampus *in vivo*, we carefully compared the input–output relationship, in terms of presynaptic activity levels versus postsynaptic potentials, before and after the induction of synaptic plasticity and found that synaptic plasticity led synapses to respond more robustly to inputs, that is, synaptic gain was increased as a function of synaptic activity with an expansive, power-law nonlinearity, i.e. conforming to the so-called gamma curve. In extreme cases, long-term potentiation and depression coexist in the same synaptic pathway with long-term potentiation dominating over long-term depression at higher levels of presynaptic activity. These findings predict a novel function of synaptic plasticity, i.e. a contrast-enhancing filtering of neural information through a gamma correction-like process. © 2006 Published by Elsevier Ltd on behalf of IBRO.

Key words: long-term depression, long-term potentiation, gamma curve, power law, synaptic transmission.

Balances of alternations in synaptic weights, such as long-term potentiation (LTP) and long-term depression (LTD), are important in improving the fidelity of behavioral output. Comprehending bidirectional synaptic modifications is, therefore, essential for understanding the reorganization of cortical functions. In contrast to LTP, the occurrence of LTD in adult animals, particularly *in vivo*, remains controversial. Homosynaptic LTD is reproducibly elicited by prolonged 1-Hz stimulation in immature hippocampal slices (Dudek and Bear, 1992; Mulkey and Malenka, 1992), but this protocol has failed to induce LTD in the adult brain *in vivo* (Errington et al., 1995; Doyle et al., 1997). Instead, the most efficient protocol to induce LTD *in vivo* seems to be repetitive low-frequency paired-pulse stimulation (LFPS) (Thiels et al., 1994; Takita et al., 1999; Nakao et al., 2004). LFPS is believed to simultaneously produce

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excitatory activation and postsynaptic inhibition (Thiels et al., 1994). In previous studies, synapse efficacy was monitored at a single baseline level, and therefore, LTD-associated changes in the input–output (I-O) relationship are not fully clarified. We started this work by carefully constructing the I-O curve at hippocampal CA1 synapses in a wide range of stimulus intensities and we then elucidated how the I-O profile is altered by the induction of synaptic plasticity.
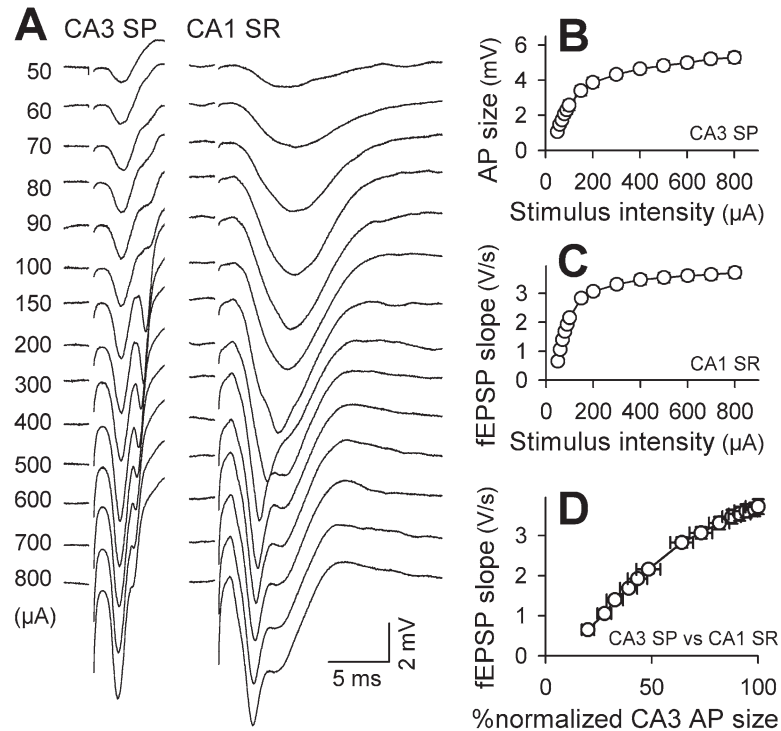
In anesthetized mice, the Schaffer collaterals, the axons of CA3 pyramidal cells, were stimulated at intensities ranging from 50 to 800 $\mu$A, and evoked field potentials were recorded from two loci, the CA3 stratum pyramidale and CA1 stratum radiatum (Fig. 1A). Assuming the uniform spatial distribution of the Schaffer collaterals in the stratum radiatum, one can consider that the size of an antidromic action potential (AP) recorded in the CA3 stratum pyramidale reflects the relative number of the Schaffer collaterals activated (Fig. 1B) and therefore is nearly proportional to the total amount of CA1 synaptic inputs. On the other hand, the slope of a field excitatory postsynaptic potential (fEPSP) reflects the number of activated synapses and their transmission efficacy (Fig. 1C). Based on this idea, we reconstructed the I-O transfer function at Schaffer collateral–CA1 synapses by comparing the CA3 AP amplitudes and CA1 fEPSP slopes (Fig. 1D).

By fixing the stimulus intensity to a point that produced 50% of the maximum control responses, we monitored the baseline responses for 30 min. Then, LFPS was applied to the Schaffer collaterals to induce LTD. During the 15-min period of LFPS, the stimulus intensity was increased up to 700 $\mu$A. As reported previously (Thiels et al., 1994; Takita et al., 1999; Nakao et al., 2004), LFPS induced LTD, which persisted for at least 120 min (66.1±4.6% of the control responses in four mice) (Fig. 2A). This form of LTD was not attributable to synaptic malfunction because it was reversible by subsequent application of theta-burst stimulation (TBS) (Fig. 2E). Surprisingly, however, when the baseline responses were monitored at a high-stimulus intensity producing the 90% of the maximum control response, the same LFPS now led to LTP (Fig. 2B, 129.1±8.9% in four mice). Therefore, LFPS only ostensibly induced LTD, but indeed, it also induced LTP in the same synaptic pathway.

We created the I-O curves before and after LFPS application to determine how LTP and LTD are co-present. We found that LTD was evident at lower input levels, but LTP became prominent as higher input levels (Fig. 2C), that is, the direction of plasticity shifts from depression to

**Fig. 1.** I-O relationship at CA3-to-CA1 synaptic transmission in anesthetized adult mice. (A) Representative traces recorded from CA3 stratum pyramidale (SP) and CA1 stratum radiatum (SR). CA1 SR was activated with a single-pulse stimulus at intensities indicated in the left column (50–800 $\mu$A). (B, C) Relationship between stimulus intensities and amplitudes of AP evoked in CA3 SP (B) or fEPSP slopes evoked in CA1 SR (C). (D) I-O curve was reconstructed from the same data as the panels B and C. The sizes of CA3 antidromic spikes were normalized to the maximum value and considered here as relative CA1 input levels. Data are represented as means±S.E.M. unless the error bars are smaller than the size of symbols ($n$=23 mice).

potentiation as the number of activated afferents increases. In contrast, the curve of stimulus intensities versus CA3 AP amplitudes was unaffected by LFPS ($P$=0.92; Kolmogorov-Smirnov test; data not shown). We therefore re-plotted these data, now relative to fEPSP slopes before LFPS as a function of CA3 AP amplitudes (Fig. 2D). In the log–log coordinate system, these parameters were almost linearly correlated across LTD and LTP ($F$=717.9, $P$<0.0001), that is, they followed the power-law equation Response≈Input$^{1/\gamma}$. In this case, the exponent $\gamma$ was 0.92. This equation, often called the "gamma curve," typified the I-O relationships of various signal transfer devices. To our knowledge, our finding is the first evidence that the power-law principle operates in activity-dependent changes in transmission efficacy in biological systems.

Are such gamma power-law modulations universal in plasticity-associated gain modifications? We sought to determine the I-O relationships in synaptic plasticity induced by three other protocols of conditioned stimuli. We first tried LFPS at a mild stimulus intensity of 400 $\mu$A. In this experiment, test stimuli were restricted in the range from 50 to 400 $\mu$A to scan the I-O curves because stimulation at more than 400 $\mu$A would recruit non-tetanized, naïve pathways. In contrast to strong LFPS, mild LFPS induced LTP in the entire range of input levels tested (Fig. 3A), but interestingly, its I-O response modulation still fit the gamma equation with $\gamma$=5.22 ($F$=214.2, $P$<0.0001; Fig.

3B). We next used TBS and high-frequency stimulation (HFS; 100 pulses at 100 Hz) at 400 $\mu$A and again found that the I-O modulation conformed to gamma power-laws with $\gamma$=1.25 and 1.61, respectively ($F$=944.7 and 459.2, both $P$<0.0001; Fig. 3C). Therefore, the gamma transfer function appears robust in synaptic plasticity-associated gain modifications.

Our findings are significant in the two following aspects. First, LFPS was thought to be a specific protocol to induce LTD *in vivo*, but in fact, it depends on the stimulus intensity used to monitor baseline responses, that is, LTD is achieved only at weaker stimulus intensities, whereas LTP becomes dominant at stronger intensities. In other words, EPSPs increase expansively as a function of stimulus intensities, as compared with pre-tetanic conditions. Because the CA3 AP size represents the approximate number of presynaptic fibers activated, i.e. the synchrony level of synaptic inputs from CA3 neurons, the data indicate that more synchronized presynaptic activities produce larger EPSP than expected from a linear extrapolation. Therefore, it can be said that synapses begin to transmit synchronized inputs more efficiently after the induction of synaptic plasticity. Synchronization of network activities is common in the hippocampus *in vivo* and considered as a powerful mechanism to convey information (Salinas and Sejnowski, 2001). Hippocampal ripple complex, in particular, is regarded as synchronous activity that represents net information to be consolidated as neocortical memory
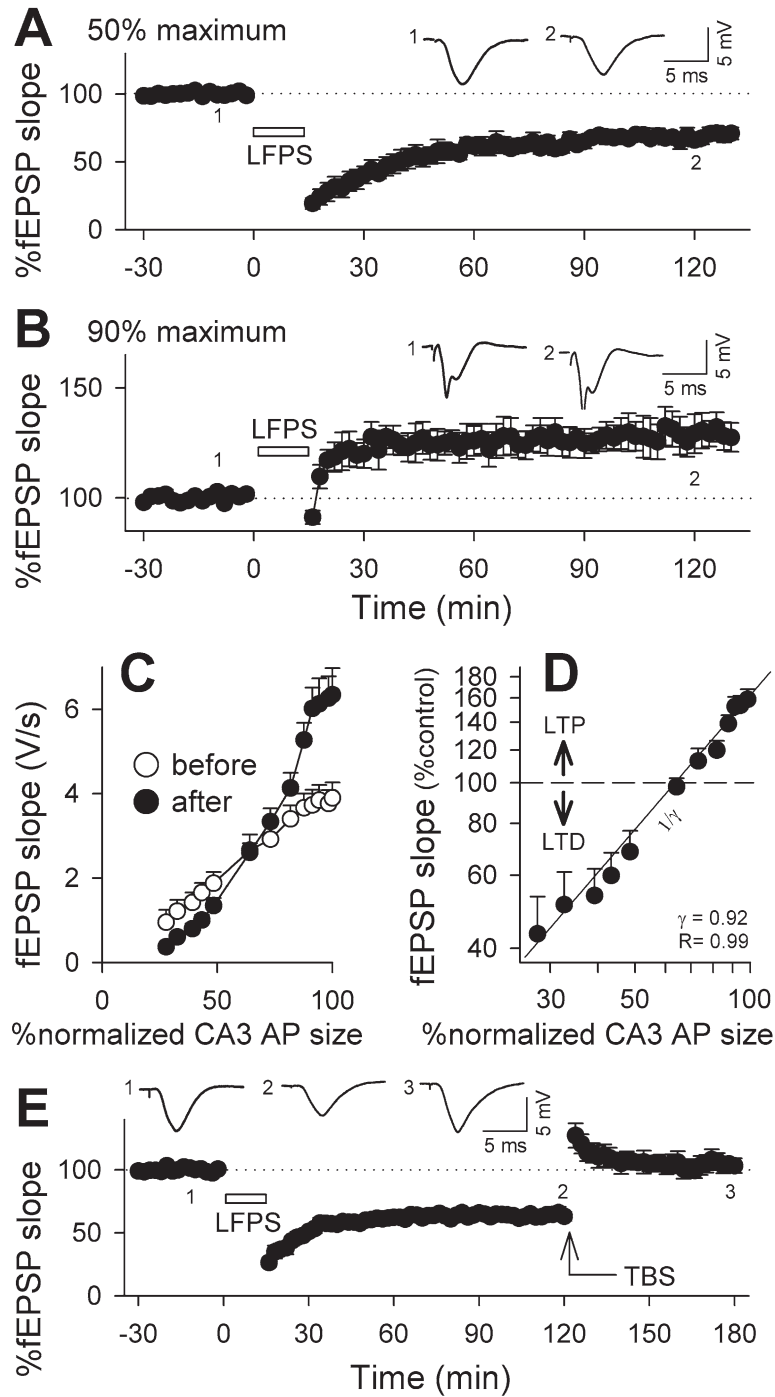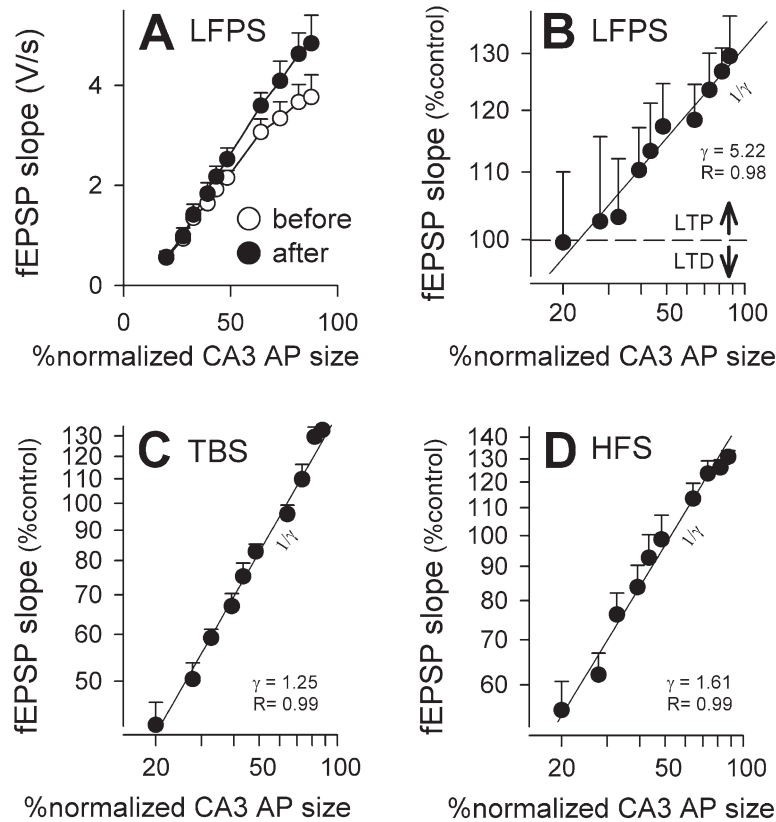
**Fig. 2.** LFPS at a strong stimulus intensity modulates the I-O curve along a gamma transfer function. (A, B) Time courses of changes in baseline responses at the 50% (A) and 90% of the maximum control response (B) (each four mice). LFPS (50 ms paired-pulse interval, 900 pairs at 1 Hz, 700 $\mu$A) was delivered during the period indicated by the open bars. Representative traces at times one and 2 are shown in the inset. (C, D) I-O curves of fEPSP slopes before (open circles) and 60 min after LFPS (closed circles) (C) were re-plotted as an after-to-before ratio in the log–log coordinate (D, $n$=8 mice). The solid line is the best linear fit to the data. (E) TBS-induced depotentiation of LTD of 50% of the maximum control response.

(Buzsaki, 1989). Synaptic plasticity could help in extracting such meaningful information.

Second, we found that the filtering properties modified by synaptic plasticity conform to the gamma curve. The gamma transfer is prevalent in a wide range of electric devices such as visual displays, and in some

cases, the gamma correction, an inverse filter that can counteract nonlinear transformation, is required to retrieve the linearity in signal transmission. If neuronal signals are intrinsically transmitted with a power-law nonlinearity as predicted theoretically (Hansel and van Vreeswijk, 2002; Miller and Troyer, 2002), synaptic plas-

**Fig. 3.** Gamma-curve modulations of the I-O relationship in various types of synaptic plasticity. (A, B) I-O curves of fEPSP slopes before (open circles) and 60 min after (closed circles) LFPS at a stimulus intensity of 400 $\mu$A (A) were re-plotted as an after-to-before ratio in the log-log coordinates (B, $n=6$ mice). (C, D) The same procedure was repeated to obtain the relative profiles in the I-O relationships induced by TBS at 400 $\mu$A (C, $n=5$) and HFS at 400 $\mu$A (D, $n=5$).

ticity-induced gain adaptation could serve like a gamma correction filter.

## EXPERIMENTAL PROCEDURES

Experiments were performed according to the animal care and experimentation guidelines of Nara Institute of Science and Technology and the Physiology Society of Japan, and the number of animals used and their suffering were minimized. Adult, male (8–10 weeks old) ddY mice (SLC Co., Hamamatsu, Japan) were anesthetized with urethane (1.25 g/kg; i.p.) and mounted in a stereotaxic apparatus. Body temperature was maintained at 37 °C with a heating pad. The Schaffer-collateral pathway (2.46 mm posterior and 2.30 mm lateral to the bregma) was stimulated by bipolar stimulating electrodes (100-$\mu$s-duration pulses), and evoked responses were recorded in the CA1 stratum radiatum (2.46 mm posterior and 2.0 mm lateral to the bregma) and the CA3 stratum pyramidale (2.46 mm posterior and 2.8 mm lateral to the bregma), as described previously (Matsumoto-Miyai et al., 2003). Baseline responses were obtained every 30 s at the stimulus intensity that elicited fEPSP slopes of 50% or 90% of the maximum control response. LFPS consisted of 900 paired pulses (50-ms-interval) given at 1 Hz. In some experiments the CA1 afferents were stimulated by HFS (100 Hz for 1 s) or TBS that consisted of 10 bursts with 10 pulses at 200 Hz, separated by 200 ms and repeated four times at 30 s. I-O curves were created by increasing stimulus intensities from 50 to 800 $\mu$A to compare the I-O profile 30 min before and 60 min after the induction of synaptic plasticity. Gamma values were estimated by the best fit to $Y=X^{1/\gamma}$, where $X$ and $Y$ represent relative antidromic AP amplitudes and fEPSP slopes, respectively. We reported the means±S.D. in all measurements.

## REFERENCES

Buzsaki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31:551–570.

Doyle CA, Cullen WK, Rowan MJ, Anwyl R (1997) Low-frequency stimulation induces homosynaptic depotentiation but not long-term depression of synaptic transmission in the adult anaesthetized and awake rat hippocampus in vivo. Neuroscience 77:75–85.

Dudek SM, Bear MF (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci U S A 89:4363–4367.

Errington ML, Bliss TV, Richter-Levin G, Yenk K, Doyere V, Laroche S (1995) Stimulation at 1–5 Hz does not produce long-term depression or depotentiation in the hippocampus of the adult rat in vivo. J Neurophysiol 74:1793–1799.

Hansel D, van Vreeswijk C (2002) How noise contributes to contrast invariance of orientation tuning in cat visual cortex. J Neurosci 22:5118–5128.

Matsumoto-Miyai K, Ninomiya A, Yamasaki H, Tamura H, Nakamura Y, Shiosaka S (2003) NMDA-dependent proteolysis of presynaptic adhesion molecule L1 in the hippocampus by neuropsin. J Neurosci 23:7727–7736.

Miller KD, Troyer TW (2002) Neural noise can explain expansive, power-law nonlinearities in neural response functions. J Neurophysiol 87:653–659.

Mulkey RM, Malenka RC (1992) Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. Neuron 9:967–975.

Nakao K, Matsuyama K, Matsuki N, Ikegaya Y (2004) Amygdala stimulation modulates hippocampal synaptic plasticity. Proc Natl Acad Sci U S A 101:14270–14275.

Salinas E, Sejnowski TJ (2001) Correlated neuronal activity and the flow of neural information. Nat Rev Neurosci 2:539–550.

Takita M, Izaki Y, Jay TM, Kaneko H, Suzuki SS (1999) Induction of stable long-term depression in vivo in the hippocampal-prefrontal cortex pathway. Eur J Neurosci 11:4145–4148.

Thiels E, Barrionuevo G, Berger TW (1994) Excitatory stimulation during postsynaptic inhibition induces long-term depression in hippocampus in vivo. J Neurophysiol 72:3009–3016.