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Original article

Computational approach to long-term potentiation in hippocampal CA1 area describes the efficacy of stimulation patterns

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Background: Long-term potentiation (LTP) is the best characterized form of enhancement in synaptic plasticity, which is a widely accepted model of learning and memory. The modification of long-term plasticity is a complex process and varies throughout synaptic events.

Objective: To investigate efficacy of electrical stimulus patterns for LTP induction where characteristics of hippocampal LTP are described by least-squares curve fitting.

Methods: In vitro hippocampal brain slice techniques were used to investigate the effects of tetanic stimulation (consisting square pulse at 100 Hz in 1 second) and theta-burst stimulation (TBS; typically consisting of 3 trains of 10 brief 100 Hz burst, 4 impulses each, interval of 200 milliseconds between bursts and repeated in 10 seconds between trains). The experimental data were modeled as three mathematical equations, polynomial form, exponential form, and power form. Curve fitting with the least-squares procedure and parameter solving were computed using the Levenberg–Marquardt method, with OriginPro 8.5 software.

Results: The stimulation intensity was 0.37 ± 0.0677 V with tetanic stimulation and 0.31 ± 0.0862 V with TBS. There were no significant differences among groups (one-way ANOVA, $p = 0.122$). TBS effectively induces LTP more than tetanic stimulation with $144.42 \pm 6.54\%$ of baseline (n = 10) and $134.88 \pm 6.92\%$ of baseline (n = 10), respectively. Moreover, curve fitting with the power form produced the best adjusted R^2 value and initial post-tetanic potentiation approximation. The polynomial model produced a small relative error with abundant residual. Therefore, the power form was a good model for LTP approximation.

Conclusion: Least-squares curve fitting could describe experimental results for investigating LTP induction under two patterns of stimuli: tetanic stimulation and TBS. We found that curve fitting with a power form is the most appropriate model for overall estimations when comparison is made with polynomial and exponential forms.

Keywords: Hippocampus, least squares curve fitting, long-term potentiation, LTP, tetanic stimulation, theta-burst stimulation

Abbreviations

LTP = Long-term potentiation
fEPSPs = Field excitatory postsynaptic potentials
PTP = Post-tetanic potentiation
HFS = High frequency stimulation

Long-term potentiation (LTP) is an enhancement of synaptic strength or synaptic plasticity that can persist for hours and perhaps even for a lifetime [1, 2]. Hippocampal LTP is a widely accepted model for learning and memory [1, 3, 4]. The induction of LTP is usually achieved with high frequency stimulation (HFS) [3, 5, 6]. Tetanic stimulation is a brief burst of HFS (100 Hz for 1 second) of an excitatory pathway that can also produce the LTP in the hippocampus [7]. Post-tetanic potentiation (PTP) is the synaptic potentiation that decays subsequent to tetanic stimulation, and arises within 10 minutes [8-10].

However, tetanic stimulation has a different pattern from the naturally occurring firing patterns of

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neurons. In response to this finding, theta-burst stimulation (TBS) was developed and appears capable of LTP induction based on the physiology of hippocampus [11]. TBS patterned mimics endogenous theta rhythms in the hippocampus that occur during some forms of learning and exploratory behavior [3].

Although tetanic stimulation and TBS are effective in increasing synaptic transmission, they are different from efficiencies and physiological relevance. In addition, there are many factors, such as frequency, number of pluses, or stimulus intensity that could alter magnitude of LTP. We therefore investigated whether a comparison of tetanic stimulation and TBS would produce differences in magnitude of the LTP in area CA1 of the hippocampus. Furthermore, LTP has been analyzed with least-squares curve fitting to describe the LTP magnitude and to approach and characterize the response of hippocampal neurons.

Materials and methods

Preparation and maintenance of brain slices

Hippocampal slices were prepared from male Wistar rats (250–450g). The animals were decapitated after anesthesia. The brains were rapidly removed from the skull and maintained in ice-cold artificial cerebrospinal fluid (ACSF) consisting of the following: 119 mM NaCl, 26.2 mM $NaHCO_3$, 11 mM glucose, 2.5 mM $CaCl_2$, 2.5 mM KCl, 1.3 mM $MgSO_4$, and 1.0 mM NaH_2PO_4, oxygenated with a 95% O_2 and 5% CO_2 gas mixture (pH 7.3–7.4). The hippocampus of both sides was then dissected out and sliced at 400 microns thickness using a vibrating tissue slicer (Vibratome Instruments). The slices were maintained for 1–2 hours, and stored in a holding chamber at 22–24°C. For the electrophysiological experiments, slices were moved to recording chambers and were immersed in ACSF at flow rate of 2.3 ml/min. All animal procedures were in full compliance with national and international standards and were approved in advance by our institutional Animal Use Committee at the Faculty of Medicine, Chulalongkorn University.

Electrical stimulation and recording

Stimulating and recording electrodes were positioned via micromanipulators in the slice under visual guidance under a microscope. Bipolar tungsten stimulating electrodes were placed into the Schaffer collateral in area CA1 (150 microns deep). For extracellular recording of field excitatory postsynaptic potentials (fEPSPs), a glass micropipette filled with 4 M NaCl (2–6 MΩ resistance) was used in the stratum radiatum of the CA1 area. The fEPSP were elicited by adjusting the stimulation intensity ranging from 0.18 V up to the intensity that yielded fEPSP of maximal slope. The position of the stimulating electrode and the recording electrode are shown in **Figure 1**.

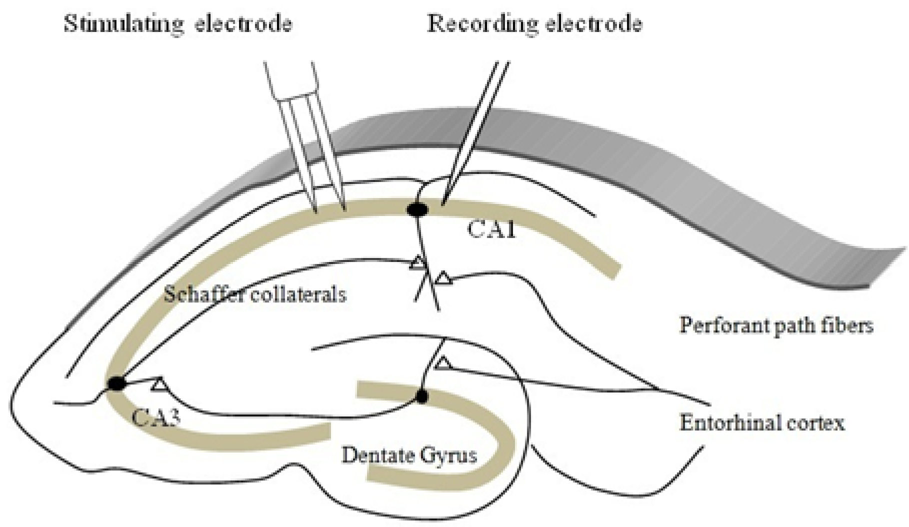


Figure 1. The electrode placement for LTP induction in area CA1 of the hippocampus.

At the start of each experiment, a single square pulse was delivered once every 10 seconds (0.1 Hz) to test the stimulus. After fEPSPs were acquired and remained stable for at least 30 minutes as the baseline level, the tetanic stimulation and TBS were applied. The tetanic stimulation consisted of 100 pulses in 1 second (100 Hz). TBS typically consists of three trains of 10 brief 100 Hz bursts, 4 impulses each, 200 milliseconds between bursts and is repeated in 10 seconds between trains as shown in **Figure 2**. For more detail consult the literature [11, 12]. Finally, we applied a 0.1 Hz test stimulus and continued recording for 60 minutes. LTP was estimated to be the change in slope of the fEPSPs.

Data obtained in the individual experiments were normalized to their respective baselines that were referenced 100%. The data are expressed as the mean values of the groups and standard errors of the mean values (mean SEM). Statistical comparisons were performed by the analysis of variance test (one-way ANOVA). The α level for statistical significance was set at p < 0.05.

Least square curve fitting

$a_0, a_1, ..., a_m$ $R^2_{adj} = 1-(1-R^2)\left(\frac{n-1}{n-p-1}\right)$

The purpose of curve fitting was to describe experimental data as mathematical equations. Data are interpreted into a recognized model $y(t, a_0, a_1, ..., a_m)$, where y is dependent variable which is measurement, t is independent variable that is controlled by the experimenter, and $(m+1)$ variables are computing parameters from data.

Let $(t_1, y_1), (t_2, y_2), \ ... \ , (t_n, y_n)$ be given n data points, least-squares curve fitting problems arise when fitting a parameterized model to real data points by minimizing the sum of squares of error between the data points and this model. Then the objective function for the minimization problem is:

$$E(a_0, a_1, ..., a_m) = \sum_{i=1}^{n} \left(y_i - y(t_i, a_0, a_1, ..., a_m)\right)^2 \quad (1)$$

The basic idea for obtaining solution is a calculus approach. Technically, the derivative of objective functions with respect to $a_i, i = 0, ..., m$ is equal to zero. Thus parameters a_i are solved and are substituted in $y(t, a_0, a_1, ..., a_m)$ as a goodness fitted model. A difference between the fitted value provided by the model and the observed value is a residual that is considered to be zero as ideally fitting. The computational methods for solving least square problems, we used Levenberg–Marquardt method, see [13, 14] with Origin-Pro 8.5 software (OriginLab, Northampton, Ma, USA).

The coefficient of determination or R^2 is a measure of effectiveness of an estimated curve fits the data, the formula as:

$$R^2 = 1 - \frac{RESS}{Total\ SS} = 1 - \frac{\sum\left(y - y_{fit}\right)^2}{\sum\left(y - \bar{y}\right)^2}, \quad (2)$$

where $RESS$ is residual sum of squares, $Total\ SS$ is total sum of squares, y is values from data, is fitted values and $\bar{y}$ is mean of data values.

The equals the proportion of the total variation in the values of the independent variable, () that can be explained by the association of with as measured by the estimated curve [15]. If converges to 1 then the curve fitting model more closely corresponds to actual data.

For completeness, we assessed the adjusted- or to compensate for practicable bias attributable to a distinct number of parameters [17] as shown in Eq. 3:

, (3)

where is sample size and is the number of parameters.

Results

The response minimum 30 minutes before tetanic stimulation and TBS were normalized and determined as a baseline response. The intensity was 0.37 ± 0.0677 V with tetanic stimulation and 0.31 ± 0.0862 V with TBS. There were no significant differences among groups we examined for stimulation intensity (one-way ANOVA, p = 0.122).

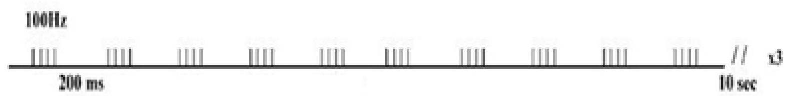


Figure 2. Theta-burst stimulation typically consisting of three trains of 10 brief 100 Hz burst, 4 impulses each, 200 milliseconds between bursts and repeated with 10 seconds between trains.

The efficacy of tetanic stimulation and TBS were represented as a percent change of baseline fEPSPs slope. PTP is record within first 5 minutes and LTP is measured from an average increase of synaptic responses in 50–60 minutes after tetanic stimulation and TBS.

The beginning of tetanic stimulation (n = 10) resulted in a large, rapidly magnifying PTP (162.85 ± 29.59% of baseline), with peak approximately 213% of baseline. The potentiation swiftly decayed over the first 5 minutes after tetanic stimulation and then continued to be stable until the end of the recording period (60 minutes after tetanic stimulation, **Figures 3a and 4a**). The LTP was 134.88 ± 6.92% of baseline.

To determine the efficacy of LTP from the pattern of stimulation, a TBS was applied (n = 10). The TBS resulted in a large, rapidly magnifying PTP (148.13 ± 13.39% of baseline), with peak approximately 193% of baseline. The potentiated response stabilized within 3 minutes after stimulation, and remained stable until the end of the recording period (**Figures 3b and 4a**). The LTP was 144.42 ± 6.54% of baseline. There was a significant difference in the magnitude of the LTP induced by tetanic stimulation and TBS ($p < 0.0001$). We found that TBS effectively induces LTP more than tetanic stimulation; this finding is illustrated in **Figure 5.**

As experimental results above, we considered three models for curve fitting. Since polynomial function is general manipulation for curve fitting because its simplicity of computing, efficient running time, and produces moderately accurate results, we chose polynomial 4$^{\text{th}}$ order model as follows for fitted data:

$$y(t) = P_0 + P_1 t + P_2 t^2 + P_3 t^3 + P_4 t^4 , \tag{4}$$

where are fitting parameters, represents % change in the slope of fEPSPs, and represents times.

However, the best model could be good explanation of experiments. For the accurate interpretation of experimental results, we concentrated on the percent changes in the fEPSPs after each pattern of stimulation for the magnitude of LTP that was found. This approach resulted in a large PTP, a majority of which swiftly decayed over the first 5 minutes, then potentiation continued to be stable until the end of the recording period (Fig. 4a, 5a). Thus, these conditions produced a second model in exponential form:

$$y(t) = A + Be^{-Ct} , \tag{5}$$

where is the % change in the slope of fEPSPs and is time. All parameters in Eq. 5 are a reasonable term for the data because parameter represents the stable line and represents the exponential decay curve.

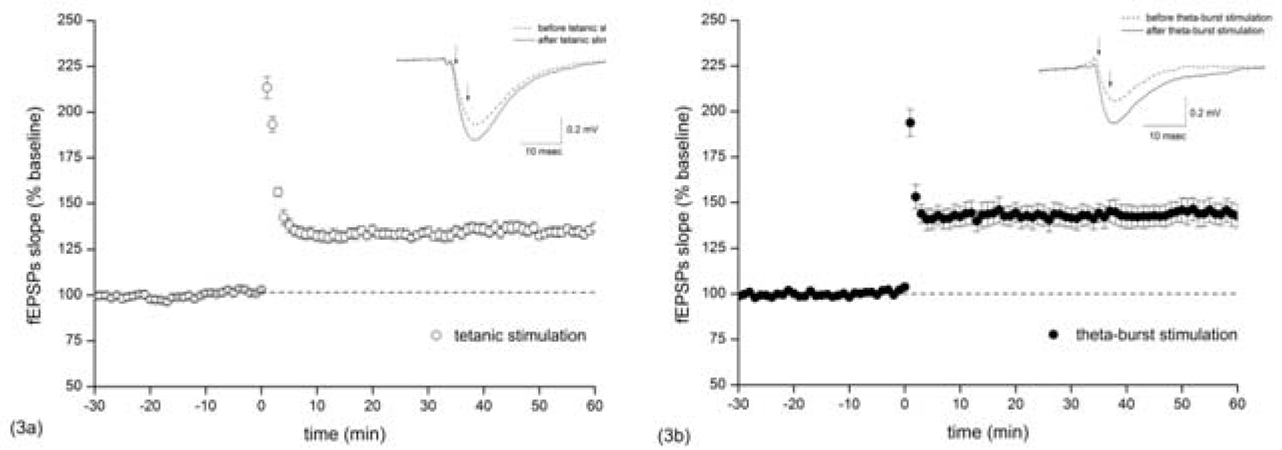


Figure 3. The fEPSPs slope results from tetanic stimulation and theta-burst stimulation. Single-pulse stimuli were delivered every 10 seconds. After a 30 minutes with a stable baseline period (time –30 to 0), either tetanic stimulation or theta-burst stimulation were applied to induce LTP at the 0 time point, and the post tetanic stimulation and theta-burst stimulation responses were continuously recorded for 60 minutes. The measurements of the fEPSP slopes were plotted, for which each point was an average over 6 values of 0.1 Hz (6 points in 1 minute). The inset shows an example of the raw fEPSPs, and the slope between the arrowhead is used for measuring fEPSP changes before and after tetanic stimulation and theta-burst stimulation. **a:** Tetanic stimulation resulted in rapidly developing LTP that decayed and then stabilized over recording period (LTP was 134.88 ± 6.92% of baseline). **b:** The theta-burst stimulation effectively induces LTP more than tetanic stimulation with 144.42 ± 6.54% of baseline.

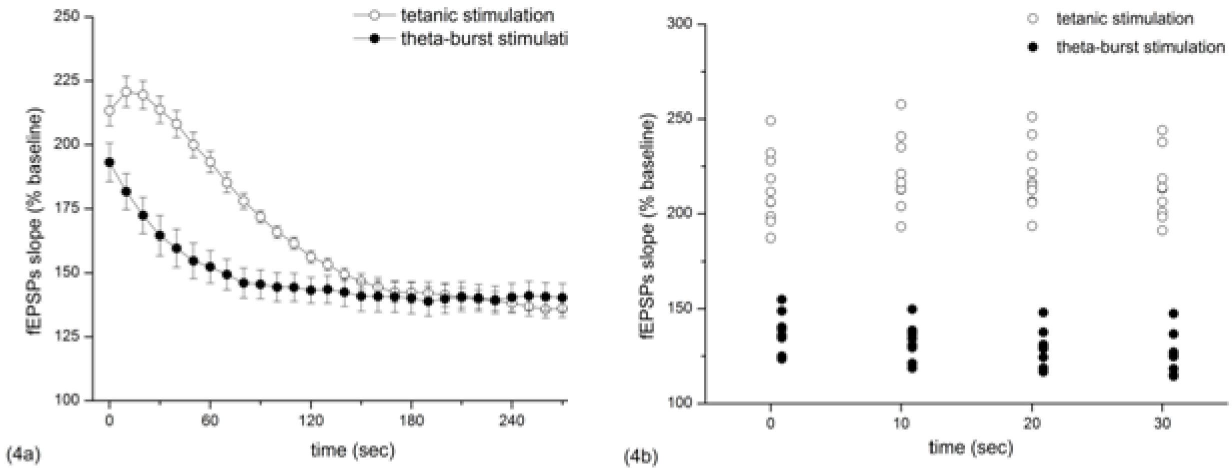


Figure 4. **a:** PTP in first 5 minutes after tetanic stimulation and theta-burst stimulation, each point plots a 10 seconds time interval. **b:** Raw data from the fEPSPs slope with n = 10 which measured across the first 30 seconds after tetanic stimulation and theta-burst stimulation.

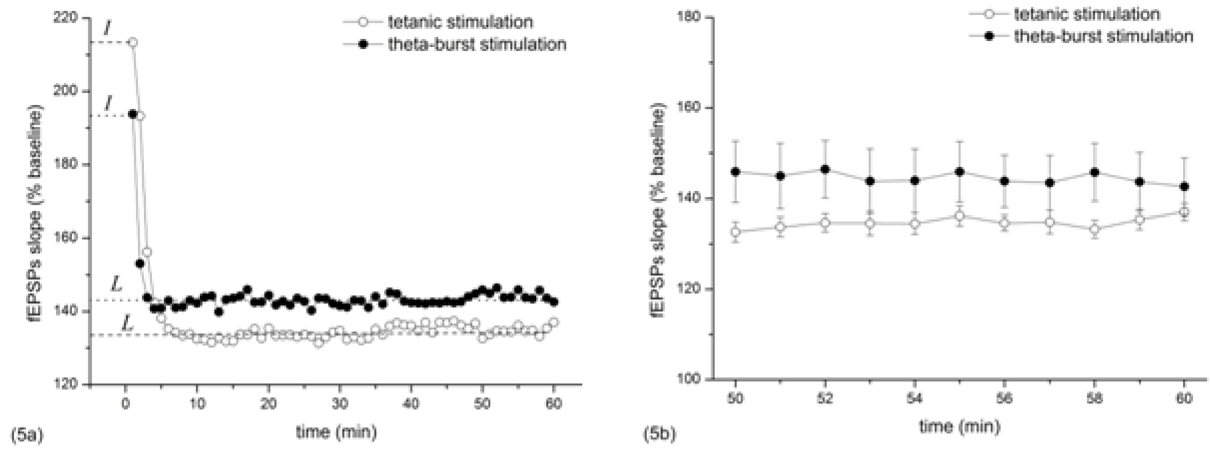


Figure 5. Summary of fEPSPs slope of tetanic stimulation and theta-burst stimulation. **a:** The fEPSPs slope in recording period (60 minutes), I and L represent initial and long-term responses respectively. **b:** Results of long-term potentiations at the final 10 minutes of recording (50–60 minutes), each point plots the average of fEPSPs slope at 1 minute intervals.

As displayed in Fig. 5a, we determined two suitable time scales for the fEPSPs slope. The initial PTP, represented by and the LTP at time 50–60 minutes, represented by . We constructed a third model with form of power function as follows:

$$y(t) = I\left(\frac{k^n}{k^n + t^n}\right) + L\left(\frac{t^n}{k^n + t^n}\right), \tag{6}$$

where is the percent change in the slope of fEPSPs, is time, and are positive parameters. The power form in Eq. 6 indicates a dominant feature of the curve in Fig. 5a. This model explained by taking the limit of , approaching and for Eq. 6, we obtain:

$$\lim_{t\to 0^+}\left(I\left(\frac{k^n}{k^n + t^n}\right) + L\left(\frac{t^n}{k^n + t^n}\right)\right) = I$$

and

$$\lim_{t\to \infty}\left(I\left(\frac{k^n}{k^n + t^n}\right) + L\left(\frac{t^n}{k^n + t^n}\right)\right) = L \quad .$$

These limit results are reasonable for experimental data interpretation. Eq. 6 was simplified to the following:

$$y(t) = \frac{Ik^n + Lt^n}{k^n + t^n}$$

$$= \frac{I\left(k^n + t^n\right) + Lt^n - It^n}{k^n + t^n}$$

$$= I + \left(L - I\right)\left(\frac{t^n}{k^n + t^n}\right)$$

Thus, the third power form model for least squares curve fitting is:

$$y(t) = I + \left(L - I\right)\left(\frac{t^n}{k^n + t^n}\right) \tag{7}$$

Note that, the model construction in Eqs. 5 and 7 are models for the nonlinear least-square curve fitting.

To solve of all parameters from Eq. 4, from Eq. 5 and from Eq. 7, and recalled from Eq. 1 ,we must minimize the function:

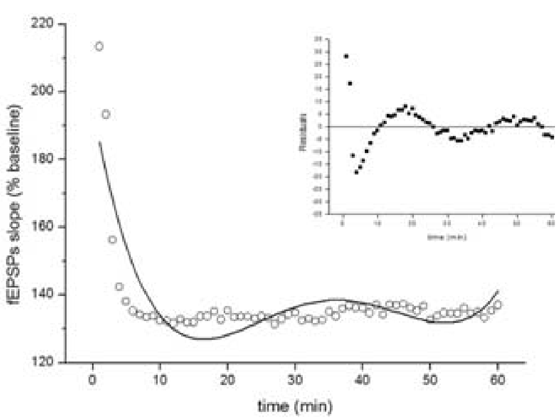
$$f = \sum_{i=1}^{n} (y_i - y(t_i))^2 , \tag{8}$$

where are the given data points. The parameters of Eq. 8 were obtained from fitting the experimental data in recording period (1–60 minutes of after tetanic stimulation and TBS) with OriginPro 8.5 software. The summary of fitting results is shown in **Table 1**. The curve fitting and residuals (difference value between experiment data and fitting) are shown in **Figures 6 and 7**.

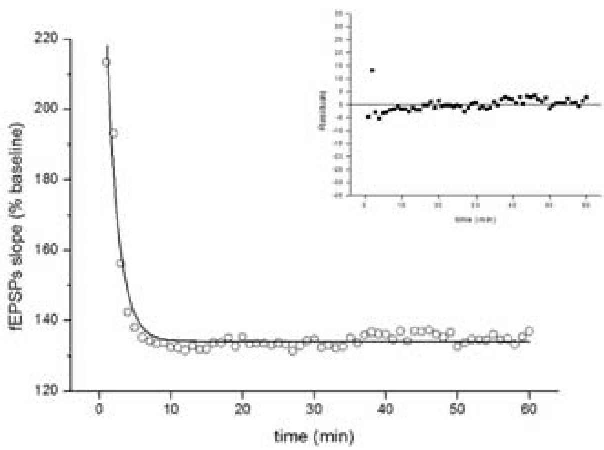
In accordance with Eqs. 4, 5, and 7, and parameters values from Table 1, these allow the calculation of functions $y(t_i)$ at arbitrary time constants and determine magnitude of LTP. The initial PTP, $y(t_1)$ was calculated by substitute $t_1 = 1$ (as y_1 in **Table 2**). To compare with real data y_i, the relative error was used as .$|(y_i - y(t_i))/y_i|$ Consequently, LTP calculated from the average of y(51), y(52), ..., y(60) and typical results from the computational model of fitting LTP are summarized in **Table 2**.

Table 1. The parameters values of least square fitting

Model	Parameters	Tetanic stimulation	Theta-burst stimulation
Polynomial	P_0	195.52647	165.99986
	P_1	–10.88533	–4.19639
	P_2	0.58624	0.22911
	P_3	–0.01227	–0.00485
	P_4	8.79114E-5	3.52476E-5
Exponential	A	134.05117	143.06938
	B	153.85253	277.08508
	C	0.60322	1.69598
Power form	I	214.52135	194.24051
	L	134.26524	143.08861
	k	2.46777	1.70749
	n	4.77765	8.94841



(6a)



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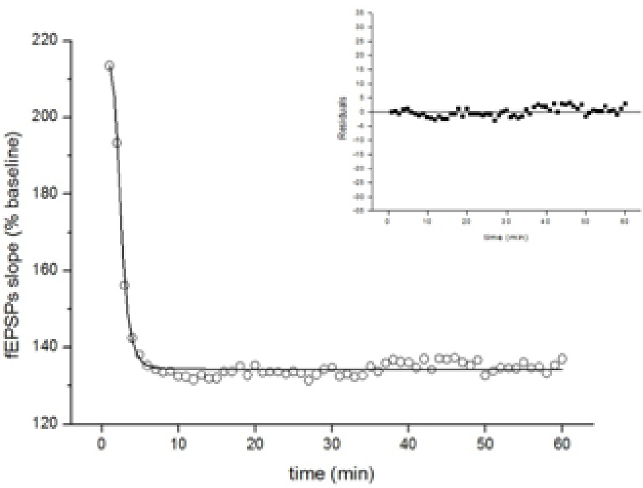
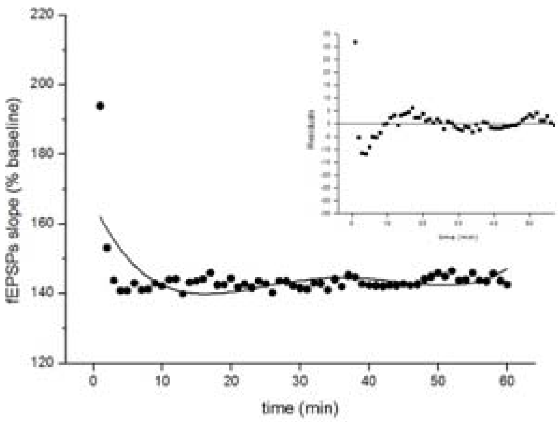


(6c)

Figure 6. The experimental results of the fEPSPs slope (% baseline) from tetanic stimulation. The lines are a curve fitted using the least squares procedure, the insets show the residual or error from curve fitting and the actual data. **a:** The polynomial model curve fitting, **b:** The exponential model curve fitting, **c:** The power form model curve fitting.



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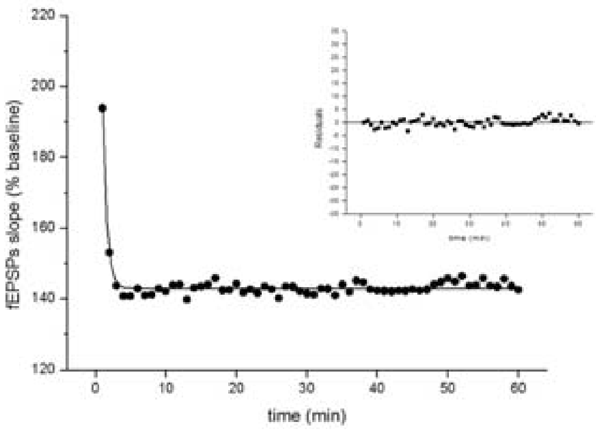

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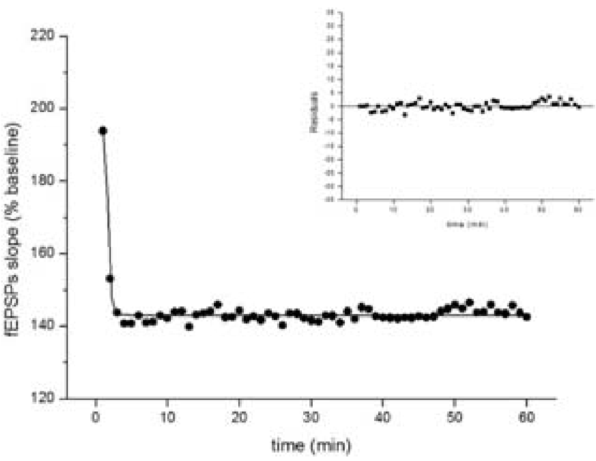

(7c)

Figure 7. The experimental results of the fEPSPs slope (% baseline) from TBS. The lines represent a curve fitted using the least squares procedure, the insets show residuals or error from curve fitting and the actual data. **a:** The polynomial model curve fitting, **b:** The exponential model curve fitting, **c:** The power form model curve fitting.

Table 2. Representative initial PTP and LTP, comparison between experimental data and computational value

	Model	R^2_{adj}	y_1	$y(t_1)-y(1)$	Relative error	LTP	Fitting LTP	Relative error
Tetanic stimulation	Polynomial	0.69836	213.36324	185.21520	0.131925	134.88271	135.04725	0.001220
	Exponential	0.95751	213.36324	218.21578	0.022743	134.88271	134.05117	0.006165
	Power form	0.98484	213.36324	213.46351	0.000470	134.88271	134.26527	0.004578
Theta-burst stimulation	Polynomial	0.32125	193.81782	162.02777	0.164021	144.42413	144.72374	0.002074
	Exponential	0.95216	193.81808	193.89216	0.000382	144.42413	143.06938	0.009380
	Power form	0.95247	193.81808	193.81782	0.000001	144.42413	143.08861	0.009247

y_1 = experimental data of initial PTP, $y(1)$= computational value of initial PTP, LTP = experimental LTP, Fitting LTP = LTP from model fitting

Discussion

The results described above reveal the effects of tetanic stimulation and TBS protocols on synaptic changes and the magnitude of LTP in area CA1 of Hippocampus. These results also provide a description of LTP using least-squares curve fitting that enabled us to distinguish between the usefulness of some LTP conditions. While tetanic stimulation has been the favored method for LTP induction, it is not relevant to natural behavior related to learning in the intact animal [4]. TBS were created that seem capable of eliciting LTP and is naturally closer to what occurs in the hippocampus during learning and memory. However, it remains unclear from several studies why the LTP magnitude for TBS tetanic stimulation is statistically different [11].

Hippocampal LTP has been studied as a cellular model of learning and memory [1, 3]. LTP is induced by brief high-frequency stimulation and TBS. Potentiation from induction is divided into three phases; post tetanic potentiation-PTP, an immediately decrease of synaptic efficacy followed by a plateau of LTP [17]. Considerable evidence now connects the increase in postsynaptic Ca^{2+} to initial steps inducing LTP [7, 11]. By contrast, PTP arising from a presynaptic accumulation of Ca^{2+} during potential induction and the accelerated decay of PTP reflects a component in removal of residual Ca^{2+} from the presynaptic terminal [8, 17].

Because initial PTP from tetanic stimulation is higher than from TBS (**Figure 4b**), it is suggested that Ca^{2+} resulting from tetanic stimulation is accumulated in the presynaptic terminal more than Ca^{2+} accumulation as a result of TBS. Similarly, the line-scatter plot for individual experiments shown in **Figure 4a**, during first 5 minutes provides some interesting observations. It seems that second and third recordings after tetanic stimulation resulted in a slightly larger response compared with first the record. This situation remained for about 30 seconds, before rapid decay and it may not be seen in the recording if stimuli proceed over a longer time course, whereas this pattern was not found after TBS. The data also suggest that TBS could remove presynaptic Ca^{2+} more rapidly than tetanic stimulation. Moreover, our results from the derivative of the fitting equations (Eqs. 4, 5, and 7), shown a decay rate of PTP that also plays a role in [Ca^{2+}], short-term plasticity, and other time-dependent properties that are involved in changes in synapses [17-19].

From an approximation of initial PTP of tetanic stimulation and TBS as in **Table 1**, the power form model gave the smallest error for. By contrast, the polynomial model produced a relatively high error, and this is consistent with the data, which produced high residuals from the fitting (**Figures 6a and 7a**). These results indicated that the approximation from the polynomial model might depart significantly from the real data. This indication fits our expectation because the exponential and power form model fit the actual PTPs, while the polynomial did not.

Although polynomial model gave the smallest relative error for the LTP description (see the relative error on the right of **Table 2**), it results in higher residuals than the other models (see the last 10 minutes in **Figures 6 and 7**, which show both the positive and negative residuals from the polynomial model). The results suggest that the minimum relative error was calculated from a deletion of positive and negative errors of approximation values. Thus, the power form model is the best approximation of LTP. Moreover, the maximum of the adjusted coefficient of determination was found to be in the power form model because the main purpose of is to describe the future outcomes on the basis of related data and the model is not specific to certain points. Together, these results show that curve fitting with a power form model is a good choice for overall estimations.

Curve fitting not only provides an approximation of values that do not appear in the data set, but also describes characteristics of the data. The power form (Eq. 7) makes it is easy to find the first potentiation and LTP from the and , respectively. In addition, the exponential form (Eq. 5) could be an approximation to the fEPSP slopes at a certain time. The LTP approximation was performed by considering a large value for . Because is close to zero when there is a very large value of , LTP could be estimated by the value of .

Our curve fitting technique showed that TBS produced greater LTP than tetanic stimulation, confirming that different types of stimulation result in different LTP magnitudes [11].

What might be the reason why TBS is more effective than tetanic stimulation in LTP induction? Research has shown that high-frequency stimulation is a conditional requirement for postsynaptic CA1 neurons being strongly depolarized [5, 11, 17]. To achieve this depolarization, tetanic stimulation must stimulate the synapse at frequencies sufficiently high enough to cause temporal summation and spatial summation of EPSP. Moreover, the high-frequency activation of the synapse is consistent with the mass of synaptic neuropeptide release, whereas LTP induction by TBS is less effective in neuropeptide release [12].

In addition, the optimal theta frequency patterned for the induction of LTP was produced from a burst interval of 200 milliseconds [20]. The observations from Hernandez et al., find that TBS produced greater LTP than 100 Hz with protocols having a pulse number up to 200 or 300 [5]. However, we used TBS with total a 120 pulses and curve fitting results show that the TBS protocol is more effective for LTP induction than tetanic stimulation. This explanation suggests specific electrical stimulation patterns have different effects on LTP.

Conclusion

In this study, we propose a least-squares curve fitting model of LTP that provides an experimental basis for investigating LTP induction under two patterns of stimuli: tetanic stimulation and TBS. We found that the curve fitting with a power form is the most appropriate model for overall estimations when compared with polynomial and exponential forms.

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