FUNCTIONAL RELATIONSHIP BETWEEN NMDA RECEPTOR-MEDIATED SYNAPTIC CURRENT DURATION AND HEBBIAN LEARNING

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Abstract

N-methyl-D-Aspartate (NMDA) receptor-mediated Hebbian learning is related to NMDA excitatory post-synaptic current (epsc) duration via Ca^{2+}-threshold for the induction of long-term potentiation (LTP) [1]. Decreasing epsc duration decreases total calcium influx and hence makes it harder to elicit LTP. This model explains developmental decrease in susceptibility to LTP with decreases in epsc duration [2, 3], and genetic enhancement of learning by overexpressing NR2B, which increased epsc duration [4]. However there are additional data that doesn't fit in this threshold model. NR2A knock-out mice have reduced LTP and learning in spite of the fact that the lack of NR2A subunit increases epsc decay time [5]. Furthermore, aged dementia patients undergoing treatment with memantine, which decreases NMDA epsc duration, showed improvement in learning and memory [6].

In an effort to resolve these inconsistencies, we formulated a model of NMDA receptor-mediated temporal correlation learning. Assuming temporal coincidence of epscs is the physiological basis of associative learning we obtained an expression for learning in terms of NMDA epsc duration. We find that learning is an inverted-U function of NMDA epsc duration. Optimal epsc duration is ~250 msec, which gives maximal LTP of 200%.

Introduction

NMDA receptors are activated by glutamate released by pre-synaptic neurons. Pre-synaptic glutamate release is a probabilistic process. Binding of glutamate to post-synaptic NMDA receptors results in a peak inward current of Na^+ and Ca^{2+} that returns to baseline with a fixed time course determined by the NMDA receptor subunit composition. NMDA receptors are heteromultimers. To date six different NMDA receptor subunits NR1, NR2A, 2B, 2C, 2D, and 3A have been cloned and characterised. The decay time constant is considerably faster in cells expressing NR1-NR2A combination than in cells expressing NR1-NR2B [7].

According to Hebbs law, temporally correlated pre- and post-synaptic activity strengthens synapses or in other words results in LTP. Synaptic activation of post-synaptic NMDA receptors is required for LTP. During NMDA epsc calcium enters dendritic spine and if a short lasting (~1 sec) threshold level of Ca^{2+} is reached then LTP can be triggered. In addition to acting as a trigger for LTP, NMDA receptor is also the locus of metaplasticity [8]. It regulates the degree of synaptic plasticity. NMDA epsc duration can modulate learning or LTP in two distinct ways: (i) Direct effect- temporal coincidence of synaptic activations that govern learning is a function of the duration of synaptic activations. For example, increasing epsc duration increases the chance of temporal coincidence of epscs. (ii) Indirect effect- changing epsc duration changes the amount of calcium entering the dendritic spine, which in turn effects LTP. Increasing epsc duration increases the total calcium influx during epsc and hence makes it more likely to exceed the Ca^{2+} threshold required to trigger LTP. During the past decade considerable support has been obtained in favour of indirect-effect. Our results suggest that epsc duration has direct influence, besides indirect-effect, on LTP thereby revealing a novel form of metaplasticity- a mechanism governing Hebbian learning.

Developmental, genetic, and pharmacological changes in NMDA epsc duration

Early during development, NMDA epsc duration decreases. In superior colliculus NMDA epsc decay time measured at 40 mV was 213 $\pm$ 57 msec in neurons from post-natal day (P) 10-15 rats and it decreased to 85 $\pm$ 37 msec in P23-33 animals [9].

Similar developmental decrease was also observed in miniature epscs. Spontaneous NMDA epscs recorded from visual cortical layer IV neurons held at –50 mV had a decay time constant of 221 $\pm$ 84 msec in P12 rats and 45.9 $\pm$ 17 msec in P35 rats [10]. NMDA epsc duration and its decrease during development are not uniform across various brain regions. In somatosensory neurons NMDA receptor epsc decay time constant measured at 40 mV decreases from 248 $\pm$ 62 msec of P3-7 rats to 113 $\pm$ 26 msec in P8-14 animals [2].

The molecular basis of these developmental changes in NMDA epsc decay time constant has been identified as the changing subunit composition of NMDA receptor. Gene expression analysis in developing neocortex found that NR2A expression increases along with the decrease in epsc duration [11]. During the transition from juvenile to adult, NR2B expression is downregulated and is correlated with the decrease in NMDA epsc duration consistent with the recombinant studies [7].

Transgenic mice overexpressing NR2B subunit have much longer NMDA epscs compared to that of wild-type mice [4]. Mutant mice lacking NR2A subunit have NMDA epsc decay time course that is slower than that in wild-type mice [12]. NMDA epsc duration can be modulated pharmacologically. Memantine, an open-channel blocker of NMDA receptor decreases epsc duration [13].

Correlation between NMDA epsc duration and LTP

During the critical developmental period susceptibility to LTP decreases along with epsc duration. In P3-7 rats which had 248 msec NMDA epsc robust (158 %) LTP could be generated at thalamacortical synapses, but hardly any (102 %) LTP in P8-14 animals which had much shorter (113 msec) NMDA epscs [2]. In visual cortex, theta burst stimulation gave 135 % LTP in P14-21 rats but did not produce substantial LTP (105 %) in rats older than P35 [3]. Transgenic mice overexpressing NR2B which increased NMDA epsc duration also had increased LTP- 200 % compared to 120 % in wild-type mice [4].

These developmental and transgenic data suggest that NMDA epsc duration and LTP be linearly related. Decreasing (increasing) epsc duration decreases (increases) LTP.

These data fit very well within the framework of Ca^{2+}-threshold model [1]. Decreasing NMDA epsc duration decreases total calcium influx and hence makes it harder to elicit LTP. This monotonic relationship between epsc duration and LTP is only a part of the complete picture that comes into view in light of the following genetic and pharmacological data.

Mice lacking NR2A subunit have reduced LTP even though absence of NR2A increases the duration of NMDA epscs [5]. NR2A knock-out mice performed poorly in learning tasks compared to wild-type mice. At the clinical level memantine, which decreases NMDA epsc duration brings about improvement in learning and memory in aged patients with dementia syndrome [6].

We now have decreased LTP with decreasing NMDA epsc duration (developmental and NR2B overexpression data), decreased LTP and learning with increasing epsc duration (NR2A knock-out data) and increased learning with decreasing duration (pharmacological data). Within the framework of calcium-threshold model of metaplasticity, NR2A knock-out and pharmacological data appear as discrepancies. In an effort to see whether these data are really an anomaly or if they can form a cohesive whole along with developmental and NR2B transgenic data, we consider the other mechanism by which NMDA epsc duration can influence LTP- direct effect.

Methods

It is clear that there is correlation between NMDA epsc duration and LTP. Is it a mere correlation or is there a direct causal relationship between epsc duration and LTP? According to Hebbs law of associative learning temporally coincident synaptic activity strengthens synapses. Since the probability of temporal coincidence of epscs depends on epsc duration, we thought that epsc duration might have a direct role in addition to the indirect role via total calcium influx during epsc in LTP and learning. We investigated this possibility by developing a minimal model of associative learning in terms of epsc duration. We assume that associative learning takes place subcellularly, i.e. temporal coincidence of epscs is the physiological basis of associative learning. In order to simplify calculations we represent epscs that decay exponentially with pulses of fixed duration given by epsc decay time. Resting

duration between two successive epscs is random since the transmitter release that switches on epscs is a poisson process. Figure 1 shows a model recording of epscs at a dendrite over time.

Results

EPSC-duration model of metaplasticity

Upon careful examination of data reviewed earlier we can predict enhancement/depression of LTP from NMDA epsc duration. Optimal epsc duration appears to be 250 $\pm$ 50 msec measured at 40 mV, which gives a maximal LTP (stimulating frequency 100 Hz) of 200 %. In other words, if epsc duration is < 250 ms, increasing it results in enhancement of LTP, if epsc duration is > 250 ms, further increasing the epsc duration results in depression of LTP. In the case of NR2B transgenic mice, wild-type had low hippocampal LTP (120 %) corresponding to epsc duration of ~120 msec. Increasing the epsc duration by overexpressing NR2B to ~270 msec enhanced LTP to ~200 %. Whereas in the case of NR2A knock-out mice, wild-type had high LTP (190 %) which corresponds to epsc duration of ~ 250 msec, deleting NR2A subunit which results in increased epsc duration decreased LTP to 125 %. Thus LTP is an inverted-U function of epsc duration.

We now develop our epsc-duration model starting with the framework of direct-effect and see if it can capture the notion of optimal epsc duration. We assume associative learning is given by the probability of temporal coincidence of epscs. Figure 1 shows the time series of epscs at a dendritic spine. Given some finite number of such time series', what is the probability of temporal coincidence of a fixed number of epscs (Figure 2)? Given that epscs have a fixed duration, the chance of epscs temporally coinciding is proportional to the duration. If epscs are of very short duration, the chance of two epscs coinciding temporally is small and it increases with duration. With large epsc duration, most-likely event will be temporal coincidence of large number of epscs; hence associations are readily formed and tend to be diffuse. Whereas with small epsc duration the likelihood of coincidence is low and the most-likely event will be associating fewer number of epscs, thereby resulting in a detailed learning. Increasing epsc duration increases the chance of two epscs temporally

coinciding and in addition the number of epscs temporally coinciding also increases (Figure 3). Thus if we increase epsc duration arbitrarily we reach a point at which epscs at all dendrites coincide temporally. Assuming learning is a function of temporal coincidence of some fixed number of epscs, we find that learning is an increasing function of epsc duration for small duration as the chance of temporal coincidence increases and it is a decreasing function of duration for large duration as the number of epscs temporally coinciding increases. Thus learning, defined as temporal coincidence of a given fixed number of epscs, is an inverted-U function of epsc duration (Figure 4). The probability of a fixed number of epscs temporally coinciding is maximal at certain epsc duration.

We provide a mathematical description of the above theory and do simple numerical calculations using the data reviewed earlier. Learning is associating a fixed number of synaptic activations, or in other words, LTP results from temporal coincidence of a fixed number of NMDA epscs. Let d be NMDA epsc duration. The probability of an epsc at a given dendrite at time t is given by (see Appendix)

$$p_t = \sum_{j=1}^{\lceil t/d \rceil + 1} \int_{(t-jd)V0}^{t-(j-1)d} [(\lambda^j x^{(j-1)} e^{-\lambda x})/ (j-1)!] \, dx$$

With stimulation frequency of 10 Hz and transmitter release probability of 0.1, we get mean duration between successive epscs, $1/\lambda$ as 1 sec. Take t = 1 sec during which there can be at most $\lceil 1/d \rceil + 1$ epscs. The probability of k synaptic epscs temporally coinciding (see also Figure 2) is given by,

$$C(k) = [M! / k!(M-k)!] \, p_t^{\,k} \, (1- p_t)^{(M-k)}$$

This C models LTP in terms of epsc duration. The inverted-U dependence of C on p_t is verified as follows,

$p_t = k/M$ when $dC/dp_t = 0$ and

$$d^2C/dp_t^{\,2}|_{p_t=k/M} = - [(M!/k!(M-k)!) * (1- p_t)^{(M-k-2)} * p_t^{\,(k-2)} * (k(M-k)/M)] < 0,$$

since $0 \leq p_t \leq 1$ and k<M.

p_t is a monotonically increasing function of d and C is an inverted-U function of p_t, therefore C is an inverted-U function of epsc duration d. We now numerically evaluate p_t for various epsc durations and then calculate the corresponding LTP (C). p_t increases monotonically from 0.004 to 0.622 as we vary epsc duration from 10 msec to 990 msec. Experimentally we saw that 250 msec epsc gives maximal LTP of 200 %, so we equate the p_t at d = 250 msec with the p_t that gives maximal C. p_t (250) = 0.2 = k/M. With this relation we can calculate C or LTP in terms of epsc duration d. Figure 5 shows the results. Under our model assumptions, increasing NMDA epsc duration from 250 msec to 500 msec decreases LTP by 30 % whereas decreasing epsc duration to 100 msec decreases LTP 100-fold.

Conclusions

We explicated a novel mechanism governing Hebbian learning. Our work reveals the direct role of epsc duration in LTP and learning by explicitly taking temporal coincidence into account. This does not imply that there is no calcium-threshold, it simply states that LTP is a function of epsc duration in addition to many other variables such as total calcium influx. According to our model there is a ceiling in addition to the threshold and LTP is induced only when the synaptic calcium influx lies within this range. It also suggests that the pathophysiology underlying dementia in aged patients is at least in part due to longer duration (compared to optimal) NMDA epsc, possibly due to loss of NR2A subunit or overexpression of NR2B. Furthermore, memantine may not bring about improvement in learning in normal population whose epsc duration is already at the optimal value. We plan to make concrete our conceptualisations, in particular, analyse pattern processing by neural networks as a function of epsc duration. Is topographic map formation in self-organising neural networks a function of epsc duration? Can changes in epsc duration act as a mechanism to prevent recoding in neural networks? Our epsc-duration theory of Hebbian learning, i.e. inverted-U dependence of learning on epsc duration can be put to detailed experimental test by pharmacologically varying NMDA epsc duration over a wide range and measuring corresponding LTP in hippocampal microcultures.

Appendix

At any given synapse dendritic spine can be in resting state (off) or in conducting state (on). In response to transmitter release from the synaptic terminal, the dendrite switches from resting state to conducting state during which epsc flows and returns to resting state after a fixed duration given by epsc decay time. Due to stochastic nature of synaptic transmission each dendrite is in off-state for a random duration; then switches to on-state; stays there for a fixed duration d and then switches back to off-state (Figure 1). This procedure repeats over time.

Consider a fixed dendrite. Let it be in resting state initially. Let $N^p(t)$ = number of transitions from off- to on-state or the number of epscs at the given dendrite in time [0, t]. Let $\{N(s): s \geq 0\}$ be a Poisson process with parameter λ. It is a pure "birth" process. The "clock" of this Poisson process is stopped when the dendrite switches to on-state i.e. during epsc. It is restarted as soon as the dendrite switches to off-state.

Let τ_n; n = 0, 1, 2, ... be the successive "birth" times of the process $\{N(s): s \geq 0\}$. That is $\tau_0 = 0$, and for n = 1, 2, ... $\tau_n = \inf\{s: N(s) = n\} = \min\{s: N(s) = n\}$. Take $\tau_n - \tau_{n-1}$, n = 1, 2, ... as independent random variables each having exponential distribution with parameter λ, then the expected time to next epsc (switch to on-state) is given by $1/\lambda$. Consequently τ_n has Gamma distribution $\Gamma(n, \lambda)$. If the dendrite is in on-state at time t, then $(\tau_j + (j-1)d) \leq t < (\tau_j + jd)$, for some j = 1, 2, ... The events $\{(\tau_j + (j-1)d) \leq t < (\tau_j + jd)\}$, j = 1, 2, ... are disjoint events. Also the number of transitions during [0, t] from off- to on-state i.e. number of epscs can't exceed $\lceil t/d \rceil + 1$ because the dendrite stays in conducting (on) state for a duration of d units during each epsc. $\lceil t/d \rceil$ means integer part of t/d. Thus

p_t = Prob (duration in on-state or epsc at time t)

$$p_t = \sum_{j=1}^{\lceil t/d \rceil + 1} \text{Prob}\left((\tau_j + (j-1)d) \leq t < (\tau_j + jd)\right)$$

$$p_t = \sum_{j=1}^{\lceil t/d \rceil + 1} \text{Prob}\left((t - jd) \vee 0 < \tau_j \leq (t - (j-1)d)\right)$$

Here $a \vee b = \max\{a, b\}$.

Since τ_j has Gamma distribution $\Gamma(n, \lambda)$,

$$p_t = \sum_{j=1}^{\lceil t/d \rceil + 1} \int_{(t-jd)\vee 0}^{t-(j-1)d} [(\lambda^j x^{(j-1)} e^{-\lambda x})/ (j-1)!]\, dx$$

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Figure legends

Figure 1. Time series of epscs. At any given instant of time either there is an epsc (on state) or not (off state). The transitions from off to on are random due to the probabilistic nature of transmitter release. On to off transitions are deterministic, the duration spent in on state is fixed and is given by epsc decay time.

Figure 2. Simultaneous recording from three dendritic spines. In a given time interval the number of epscs at different synapses is not same due to stochastic nature of synaptic transmission but the duration of epscs is fixed.

Figure 3. Number of epscs most-likely to temporally coincide as a function of epsc duration.

Figure 4. Learning given by the probability of temporal coincidence of a fixed number of epscs as a function of epsc duration.

Figure 5. Hebbian learning (C) and NMDA epsc duration (d). Learning/LTP is an inverted-U function of epsc duration.

Figure 1

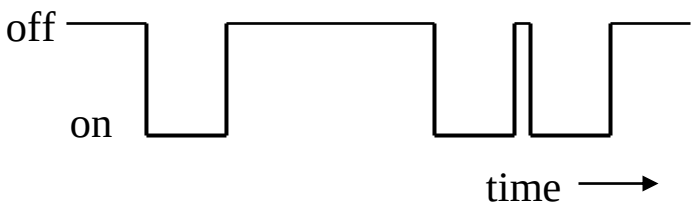

Figure 2

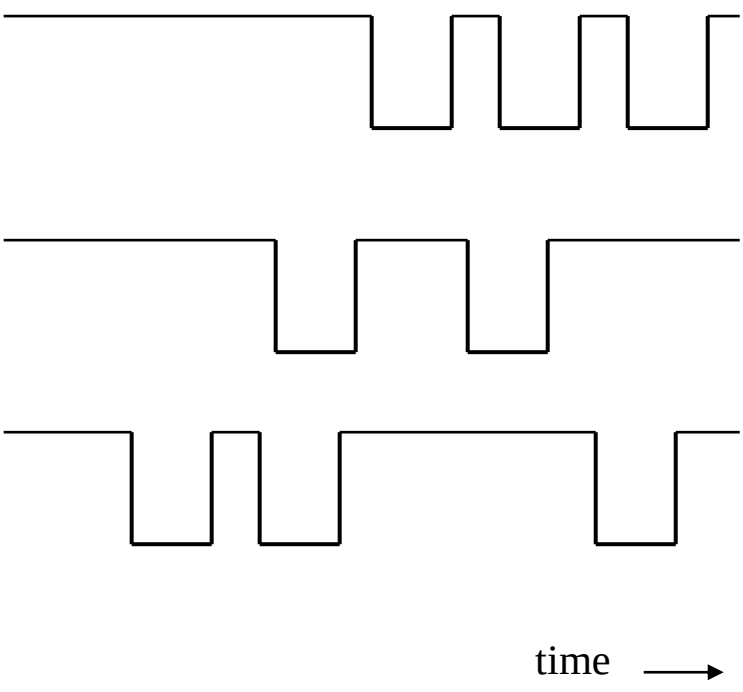

Figure 3

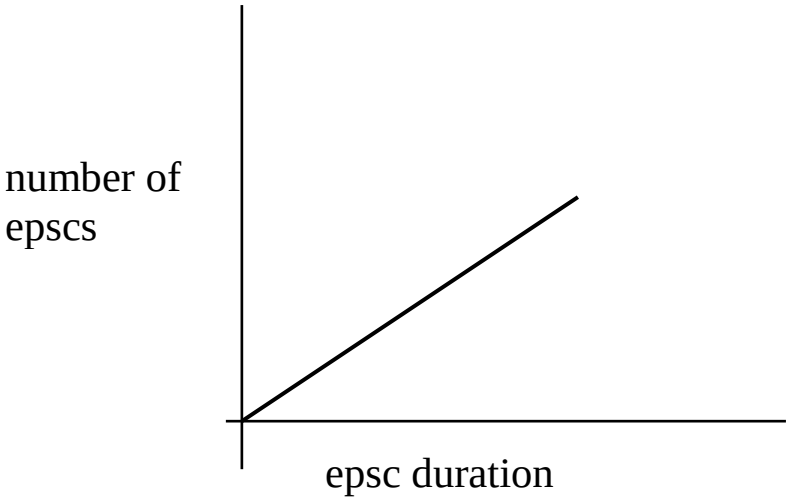

Figure 4

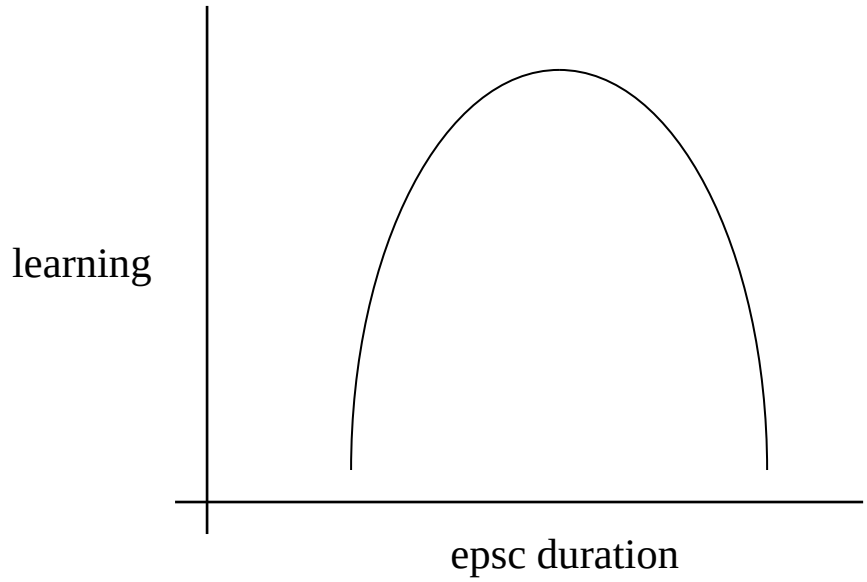

Figure 5