PERGAMON

Neuropharmacology 37 (1998) 489–500

NEURO PHARMACOLOGY

Potential for multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses

Henry Markram *, Dimitri Pikus, Anirudh Gupta, Misha Tsodyks

Department of Neurobiology, The Weizmann Institute for Science, Rehovot, 76100, Israel

Accepted 12 March 1998

Abstract

Recent experimental evidence indicates that in the neocortex, the manner in which each synapse releases neurotransmitter in response to trains of presynaptic action potentials is potentially unique. These unique transmission characteristics arise because of a large heterogeneity in various synaptic properties that determine frequency dependence of transmission such as those governing the rates of synaptic depression and facilitation. A theoretical analysis was therefore undertaken to explore the phenomenologies of changes in the values of these synaptic parameters. The results illustrate how the change in any one of several synaptic parameters produces a distinctive effect on synaptic transmission and how these distinctive effects can point to the most likely biophysical mechanisms. These results could therefore be useful in studies of synaptic plasticity in order to obtain a full characterization of the phenomenologies of synaptic modifications and to isolate potential biophysical mechanisms. Based on this theoretical analysis and experimental data, it is proposed that there exists multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses. Finally, it is shown that the impact of changing the values of synaptic parameters depends on the values of the other parameters. This may indicate that the various mechanisms, phenomena and algorithms are interlinked in a 'synaptic plasticity code'.

1. Introduction

Changing the gain of synaptic transmission has been at the center of a vast number of experiments aimed at understanding the cellular substrate of information processing, learning and memory (for reviews see Hebb, 1949, Teyler and Fountain, 1987, Morris et al., 1988, Bliss and Collingridge, 1993, Jodar and Kaneto, 1995, Maren and Baudry, 1995, Cruikshank and Weinberger, 1996, McEachern and Shaw, 1996). An assay of the impact this concept has on the field is the extent to which it has been incorporated into adaptive models of information processing (for reviews see Hebb, 1949, Amit, 1989, Sutton and Barto, 1990, Hertz et al., 1991, Churchland and Sejnowski, 1992, Fregnac and Shulz, 1994, Gluck and Myers, 1997). The importance of a long known property of synaptic transmission, frequency-dependent synaptic transmission (Feng, 1941, Hutter, 1952, Liley and North, 1953, del Castillo and Katz, 1954, Liley, 1956, Takeuchi, 1958, Hubbard, 1963, Thies, 1965, Betz, 1970, Zucker, 1989) has largely been overlooked. Frequency dependence dictates that each action potential (AP) is not transmitted in the same manner during irregular presynaptic AP activity which is typical of discharge patterns in vivo (Softky and Koch, 1993; Fig. 1). Perhaps the best characterization of the cellular substrate for learning and memory and simple behavior, carried out to date, is for the gill-withdrawal reflex in *Aplysia* which specifically involves a consideration of frequency-dependent synaptic transmission (Castellucci et al., 1970; Pinsker et al., 1970, Byrne, 1978, Carew et al., 1981, Gingrich and Byrne, 1985, Buonomano et al., 1990, Ciaccia et al., 1992). These studies and a simple consideration of the transmission properties of frequency-dependent synapses, indicate that several parameters govern transmission in complex ways other than a linear scaling of synaptic gain.

Typically, studies of synaptic plasticity are centered around a debate on which is the right mechanism for long-term potentiation (LTP) or depression (LTD) of the strength of synapses (for reviews see McNaughton, 1982; Teyler and Discenna, 1984, Siegelbaum and Kan-

* Tel.: +972 89343179; fax: +972 89344131; e-mail: bnmark@weizmann.weizmann.ac.il.

0028-3908/98/$19.00
PII: S0028-3908(98)00049-5

del, 1991, Bliss and Collingridge, 1993, Stevens, 1993, Barnes, 1995, Kullman and Siegelbaum, 1995, Maren and Baudry, 1995, McEachern and Shaw, 1996). However, recent experiments reveal a large heterogeneity in all synaptic parameters that determine the absolute strength as well as the frequency dependence of transmission at single synapses formed by the same axon (Murthy et al., 1997, Markram et al., 1998) alluding to multiple mechanisms, phenomena and algorithms for synaptic plasticity at single synapses. A theoretical study was therefore undertaken to explore the phenomenologies of pointed synaptic modifications and to consider the possible biophysical mechanisms. The results indicate that a thorough experimental characterization of synaptic modifications is essential not only to reveal the potential mechanisms that generate synaptic changes, but to understand the function of synapses in information processing and the importance of synaptic modifications in learning and memory.

2. Methods

2.1. Slice preparation

Sagittal slices (300 μM) were cut from the neocortex of Wistar rats (13–15 days) as described in (Markram et al., 1997a). Experiments were performed at 30–32°C. The extracellular solution contained (in mM); 125 NaCl, 2.5 KCl, 25 Glucose, 25 $NaHCO_3$, 1.25 NaH_2PO_4, 2 mM $CaCl_2$ and 1 mM $MgCl_2$. Layer 5 pyramidal neurons from the somatosensory cortical area were identified using infrared differential interference contrast video-microscopy on an upright microscope (Zeiss-Axioskop-FS, fitted with 40X-W/0.75NA objective) as previously described (Markram et al., 1997a). Somatic whole-cell recordings (10–20 mΩ access resistances) were obtained and signals were amplified using Axoclamp-2B amplifiers (Axon Instruments) and captured on computer using Pulse Control (by Dr R. Bookman and colleagues, Miami University) and analyzed using programs written in Igor (Igor Wavemetrics, Lake Oswego, OR, USA). Neurons were recorded with pipettes containing (in mM): 100 K-gluconate, 20 KCl, 4 ATP-Mg, 10 phosphocreatine, 0.03 GTP, 10 HEPES and 0.5% biocytin (pH 7.3, 310 mOsm). Resting membrane potential levels were typically -62 ± 2 mV.

2.2. Modeling frequency-dependent synapses

Synaptic depression was previously modeled with three parameters (absolute synaptic efficacy (A); utilization of synaptic efficacy (U) and recovery from depression (τ_{rec}) (Tsodyks and Markram, 1997). The model is based on earlier concepts of the refractoriness of the release process (see Betz, 1970, Byrne, 1978) which can be rephrased by stating that the fraction (U) of the synaptic efficacy utilized by an AP becomes instantaneously unavailable for subsequent use and recovers with a time constant of τ_{rec}. The fraction of available synaptic efficacy is termed R. A facilitating mechanism is included in the model as a pulsed increase in U by each AP. The running value of U is referred to as u while U remains a parameter that applies to the first AP in a train. The value of u decays with a single exponential, τ_{facil} to its resting value U. The amplitude of the pulsed change in u is assigned the value $U(1-u)$ which also ensures that $u < 1$.

From a resting state of the synapse, all the synaptic efficacy is available and the fraction that remains immediately after the first AP in a train is:

$$R_1 = 1 - U \tag{1}$$

During the AP train, each presynaptic AP utilizes further fractions of R at the time of its arrival. R therefore constantly changes because of subsequent utilization by APs, recovery of the unavailable synaptic efficacy with a time constant of τ_{rec}, and the pulsed increase in u caused by each AP. R for consecutive APs in the train is then,

$$R_{n+1} = R_n(1 - u_{n+1})\exp\left(\frac{-\Delta t}{\tau_{rec}}\right) + 1 - \exp\left(\frac{-\Delta t}{\tau_{rec}}\right) \tag{2}$$

where Δt is the time interval between nth and $(n+1)$th AP and where,

$$u_{n+1} = u_n \exp\left(\frac{-\Delta t}{\tau_{facil}}\right) + U\left(1 - u_n \exp\left(\frac{-\Delta t}{\tau_{facil}}\right)\right) \tag{3}$$

The synaptic response that is generated by any AP in a train is therefore given by,

$$EPSP_n = A \cdot R_n \cdot u_n \tag{4}$$

Synaptic connections displaying depression are characterized by negligible values of t_{facil} and hence $u_n = U$.The steady-state value of R (R_{st}) for a given frequency (r) of stimulation is given by;

$$R_{st}(r) = \frac{1 - \exp(-1/r\tau_{rec})}{1 - (1 - u_{st}(r))\exp(-1/r\tau_{rec})} \tag{5}$$

where;

$$u_{st}(r) = \frac{U}{1 - (1 - U)\exp(-1/r\tau_{facil})} \tag{6}$$

2.3. Stimulation protocols to examine frequency-dependent synaptic transmission

In order to examine frequency-dependent synapses in a quantitative manner it is possible to examine only the averaged response to a high frequency train of APs (Markram and Tsodyks, 1996, Markram, 1997,

Markram et al., 1998, Tsodyks and Markram, 1997). Measuring mean excitatory postsynaptic potentials (EPSPs) during high frequency trains are performed by subtracting an exponentially decaying trace, extrapolated to resting potential, to correct for the decaying voltage of the preceding EPSP. This is only a minor correction for depressing synapses, but can be considerable for facilitating synapses. Iteratively changing the model parameters allows an optimal fit to be obtained. Voltage responses are simulated in a 'point neuron', with an arbitrary input resistance and an experimentally determined membrane time constant (typically from 20 to 60 ms). Optimal fitting is achieved by minimizing an error function, E. Each EPSP is weighted to produce a contribution to an error function defined as the percent difference in $EPSP_{experiment}$ and $EPSP_{predicted}$.

$$\text{Total} \quad E = \sqrt{E_1^2 + E_2^2 + ...E_n^2}$$

where E_1 to E_n represents the error contribution of each EPSP in the train. The iteration then yields the value of the model parameters A, U,τ_{rec} and τ_{facil}.

2.4. Biophysical correlates of the synaptic parameters of the phenomenological model

2.4.1. The parameter A:

A is equivalent to the quantal size multiplied by the number of release sites and an electrotonic attenuation factor. Current-clamp recordings from the soma yield A as far as the soma is concerned. This measure of the absolute synaptic strength reflects the potential of the synaptic input to directly influence the discharging of an AP. Perfect voltage-clamp recordings would reveal A at the synapses, which is biophysically relevant to determine the average quantal size.

2.4.2. The parameter U:

U would be equivalent to the probability of release (Pr) provided it can be established that the mechanism of frequency dependence is located purely presynaptically. If postsynaptic receptor desensitization contributes to frequency dependence, then the kinetics of depression are not only determined by Pr. In addition to factors that relate to the activation of postsynaptic receptors, considerable changes in the membrane potential during high frequency stimulation of, for example, strongly facilitating synapses with large absolute synaptic efficacies, may result in the activation of voltage-dependent conductances or receptors as well as engage passive non-linearities (e.g. effect of approaching the reversal potential) which would also contribute to the value of U in current-clamp, but not in voltage-clamp experiments. Alternating voltage-clamp and current clamp experiments can therefore be employed to determine the contribution of ionic conductances to the voltages of synaptic input. Most single axon synaptic responses are moderate and do not activate voltage-dependent conductances that significantly contribute to the kinetics of changes in successive EPSP amplitudes (Markram, 1997). U is therefore a functional parameter that relates to the specific properties of the frequency dependence expressed by the connection between two neurons.

2.4.3. The parameter τ_{rec}:

τ_{rec} can be determined directly from the experimental traces and used to constrain the model fitting procedure. The biophysical correlate of recovery from depression could be vesicle depletion (Liley and North, 1953, Zucker, 1989) or recovery from a functional refractory period of release due to, for example, sequential decrease in AP-evoked Ca^{2+} influx (Klein et al., 1980, Zucker, 1989) or desensitization of the Ca^{2+}-induced release machinery. Perhaps only very slow rates of recovery from depression induced by intense activity are due to vesicle depletion (Ceccarelli and Hurlbrut, 1980, Brodin et al., 1997), while a functional refractory period determines fast recovery from depression.

2.4.4. The parameter τ_{facil}:

The biophysical basis of facilitation has been studied extensively (Magleby and Zengel, 1982, Zucker, 1989), mostly pointing to residual Ca^{2+} in the terminal as a general mechanism. The specific mechanisms underlying the various time constants for facilitation, however, are less clear (see Magleby and Zengel, 1982). Data from the neuromuscular junction suggest that the parameter, τ_{facil} could represent an average over the first two faster time constants of facilitation and part of augmentation (Magleby and Zengel, 1982).

2.5. Advantages and disadvantages of the phenomenological approach

The primary disadvantage of the phenomenological approach is that it deals only with averaged responses while quantal analysis actually attempts to resolve the statistical properties of trail to trial fluctuations. The analysis therefore yields the total quantal response and in order to determine the average quantal size per bouton would require correlated morphological analysis to determined anatomical n and simulations to normalize for differences in electrotonic distances. The average Pr can also not be derived unless the frequency-dependence is mediated purely presynaptically. Another important problem of the phenomenological model is that the biophysical correlates of the synaptic parameters become progressively less reliable as the synaptic responses approach linearity. In other words, if a synapse has a Pr of 0.5 and no synaptic depression then U will be 1. In this case the U parameter has no real

functional significance since the model is only valid when synaptic responses display frequency dependence.

Nevertheless, while the phenomenological approach clearly is not intended nor sufficient to replace classical statistical analysis of fluctuations, it can provide significant advantages over the statistical approach and ultimately the optimal approach will be a combination of both approaches. First, the difficulty of reliably recording and measuring single sweep responses is overcome since only the average response to high frequency trains is required for the analysis. Second, the phenomenological approach allows in depth analysis of frequency-dependent responses without debatable assumptions of the release process required in the statistical analyses of single sweep responses (see Faber and Korn, 1991). This allows a separation from the precise biophysical mechanisms of release-a full understanding of which is likely to evolve at the rate of molecular characterization of the building blocks of the presynaptic terminal. This separation therefore enables further studies aimed at linking synaptic transmission to information processing and synaptic plasticity to learning and memory. Third, a full characterization of the phenomena that are produced by synaptic modifications can point to the most likely biophysical mechanisms that underlie the change.

3. Results

A phenomenological model of frequency-dependent synaptic transmission (Fig. 2; see Methods) was used to examine the phenomena that would be generated by specific synaptic modifications. The primary synaptic parameters are the absolute synaptic efficacy (A), the utilization of synaptic efficacy (U), recovery from depression (τ_{rec}) and the recovery from facilitation (τ_{facil}). The most likely biophysical mechanisms underlying changes in the value of these synaptic parameters are also considered.

3.1. Distinction between depressing and facilitating synapses

It is usually assumed that whether synaptic responses display facilitation or depression simply depends on Pr (see Zucker, 1989). While Pr levels can determine the functional expression of facilitation and depression, several lines of evidence, including the modeling of these synapses, suggests that some synapses lack a strong facilitatory mechanism and hence that some depressing synapses are distinct from facilitating synapses. First, depression is observed at all synaptic connections between layer 5 pyramidal neurons even though U varies from 0.1 to 0.95 (Markram and Tsodyks, 1996, Tsodyks and Markram, 1997). For these connections, the quantal model has also been applied to asses the range of Pr (0.1–0.9) (Markram et al., 1997a). Second, when the external $[Ca^{2+}]$ is lowered to significantly reduce Pr and hence the average amplitude of the first EPSP in a train, no significant facilitation is revealed ($n = 14$; Fig. 3). Third, including facilitation into the model does not improve the fit to experimental traces (expected to fit better especially the transition EPSPs; i.e. the second and latter responses before steady-state is reached) even when U is very low suggesting that facilitation is essentially absent at these connections. This does not necessarily mean that the biophysical properties of the release machinery are different since the distinction could arise from, for example, differences in the Ca^{2+} buffering capacity within the terminals resulting in different intra-terminal

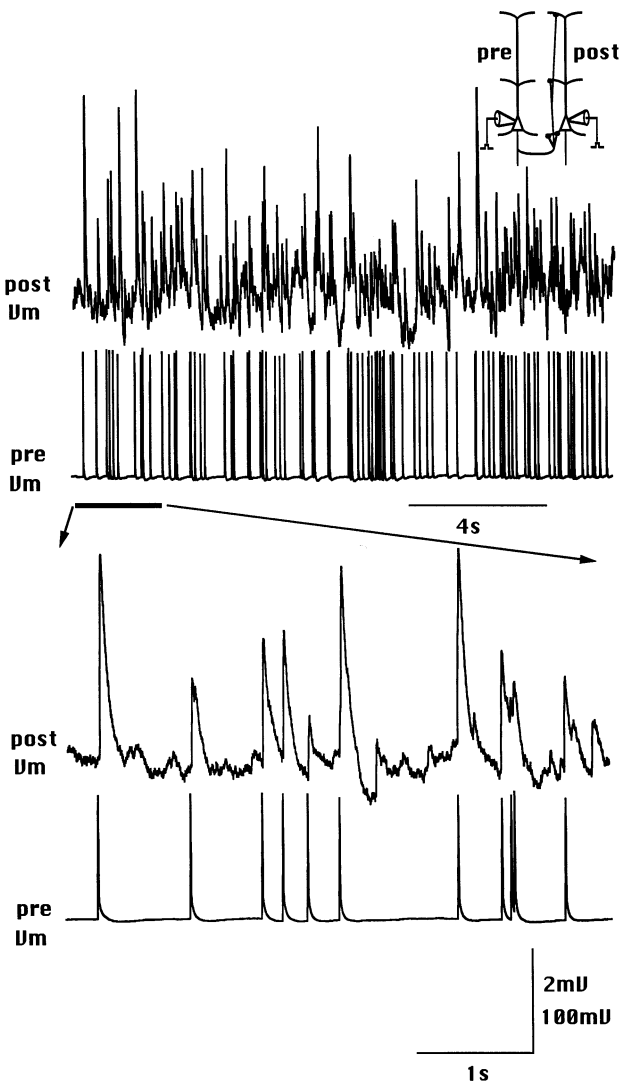

Fig. 1. Synaptic transmission of irregular presynaptic AP activity. The average discharge rate is 10 Hz. Two thick tufted layer 5 pyramidal neurons were recorded (represented schematically in the upper right corner). The synaptic connection is typical of a depressing synaptic connection. The lower panel represents the activity during the time period indicated by the solid bar.

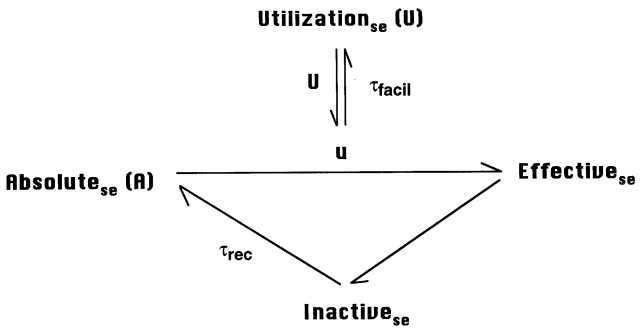

Fig. 2. Phenomenological model of frequency dependent synaptic transmission. Each AP utilizes (U) a fraction of the available/recovered synaptic efficacy (R). When an AP arrives, U is increased by an amplitude of U^f and becomes a variable, U^1. In the simulations, the value of U^f is the same as U. Depressing synapses can be simulated either by making U very large or by making τ_{facil} very small.

basal [Ca^{2+}]. In this case, depressing synapses would be analogous to facilitating synapses operating in a maximally facilitated state. Experimentally it then becomes important to distinguish depressing synapses from high Pr facilitating synapses. High Pr facilitating synapses can be distinguished from pure depressing synapses by monitoring the recovery response following a high frequency train of presynaptic APs (Fig. 4).

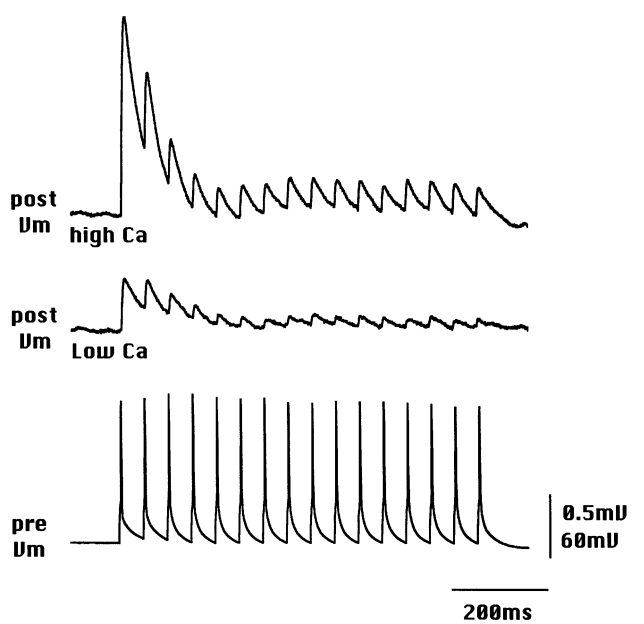

Fig. 3. Lowering Pr does not reveal facilitation at depressing synapses between pyramidal neurons. A connection between two layer 5 pyramidal neurons. Each trace represents and average of 40 trials. the presynaptic APs were delivered at 20Hz. The upper trace was obtained during the perfusion of the slice with 2 mM Ca^{2+} and 1 mM Mg^{2+} and the lower trace was obtained with 1 mM Ca^{2+} and 2 mM Mg^{2+} in the solution. The U parameter for the high Ca^{2+} condition was 0.77. Lowering Ca^{2+} failed to reveal facilitation.

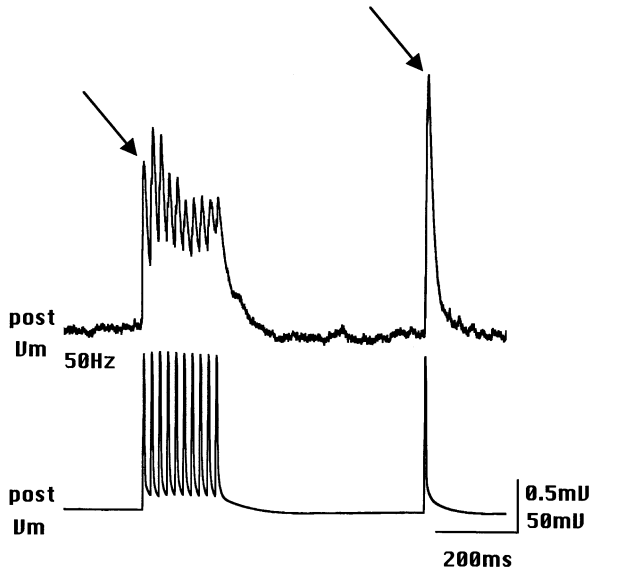

Fig. 4. High Pr facilitating synapses. A connection from an excitatory interneuron to another interneuron in layer 4. Due to a high U, the synaptic response displays depression during the high frequency train, but the facilitation is revealed, after a 500 ms rest period before the next presynaptic AP. $U = 0.37$, $\lambda_{rec} = 125$ ms, $\lambda_{facil} = 500$ ms.

3.2. Changing the number and efficacy of postsynaptic receptors at single synapses

Modulation of postsynaptic receptor efficacies has been reported as a mechanism to modify synaptic strength (McNaughton, 1982, Kauer et al., 1988, Bashir et al., 1991). Indeed, potentiating or augmenting receptor efficacies is an unambiguous potential mechanism to change synaptic strength since a uniform, frequency-independent change in all synaptic responses would be observed. Using the phenomenological model, this can be quantified as an increase in A (Fig. 5). The potential phenomena could be referred to as, for example, LTP_a and LTD_a. Depending on the persistence of memory traces, a more precise categorization into short, medium and long term changes may be appropriate (see Dudai, 1989). Changes in A need to be confirmed by monitoring the change in synaptic transmission to an irregular (Poisson) train of afferent stimuli (Fig. 5(C, D)) since it is possible that the change only appears uniform for the particular frequency used in the test pulse. This is especially important for facilitating synapses (see below). Adding more receptors will not necessarily increase A since quantal size is also limited by the amount of transmitter released. If sufficient transmitter is released to saturate the receptors then adding more postsynaptic receptors would increase A. If receptors are not saturated then A could still be changed by rearranging the clustering of receptors in the postsynaptic membrane to allow better exposure to the available neurotransmitter (Xie et al., 1997).

Postsynaptic receptor desensitization could be important during high frequency stimulation (Jonas et al., 1994, Jonas and Spruston, 1994, Jones and Westbrook, 1996) depending on whether the recovery from desensitization is slower than the recovery from presynaptically mediated depression. If postsynaptic receptor desensitization contributes towards synaptic depression, then adding receptors could change A provided receptors are saturated. Both A and U would change if the receptors are not saturated. Conditions where receptors are far from saturation or where receptors recover rapidly from desensitization could be an important part of the mechanism of facilitation, since facilitated transmitter release would require an 'endless' source of postsynaptic receptors to fully express facilitation of synaptic transmission. This is could be more important if multivesicular release occurs during facilitation (see Korn et al., 1994, Tong and Jahr, 1994). The possible effects of re-arranging the clustering of postsynaptic receptors (Xie et al., 1997) is also not trivial since the functional expression of frequency dependence could be affected in addition to changing A. Determining whether receptors are saturated and whether there is any postsynaptic component of frequency dependence is therefore an absolute requirement for understanding the effects of changing postsynaptic receptor numbers and distributions.

Similar rules could apply to selective potentiation and insertion of sub-types of receptors, such as NMDA receptors (Bashir et al., 1991). In the case of changing the numbers of NMDA receptors, if frequency dependence is influenced by recovery from NMDA receptor desensitization, then adding more NMDA receptors may cause a voltage-dependent change in U as well as an increase in A. Examining the voltage dependence of frequency-dependent transmission could therefore allow determination of the involvement of NMDA receptor desensitization in frequency-dependence and may provide a means of detecting the insertion of NMDA receptors into the postsynaptic membrane.

3.3. Changing the number of synaptic connections, active sites per connection and unmasking silent synapses

Changing the number of sites where neurotransmitter can release and activate postsynaptic receptors represents a mechanism of effectively increasing the maximal pool of activatable receptors and therefore constitutes a powerful potential mechanism of changing the absolute strength of synaptic connections. This will result in a change in A, but since it seems unreasonable that the opening of new active sites within a single terminal or a newly matured synapse, would be accompanied by an exact jump to the mean of the kinetic parameters of the other synapses/release sites of the connection, it is most probable that this form of structural change would, at least initially, be accompanied by changes in U, τ_{rec} and τ_{facil}. Phenomenologically, synaptic responses at all frequencies will be altered, but not necessarily uniformly. Unmasking silent synapses (Liao et al., 1995) by the insertion of postsynaptic receptors at synapses that have a functional release machinery, would express as an increase in A.

3.4. Changing neurotransmitter release probability

Changing Pr has been at the center of the pre versus postsynaptic debate for the mechanism of LTP. Changing Pr, however, can not change the gain of transmission uniformly for all frequencies and it is therefore misleading to consider this as a mechanism for changing the gain of transmission unless it is known, for example, that AP coding principles do not involve high frequency transmission. The phenomenon produced when Pr changes is readily distinguished from virtually all other types of synaptic changes since changing Pr is

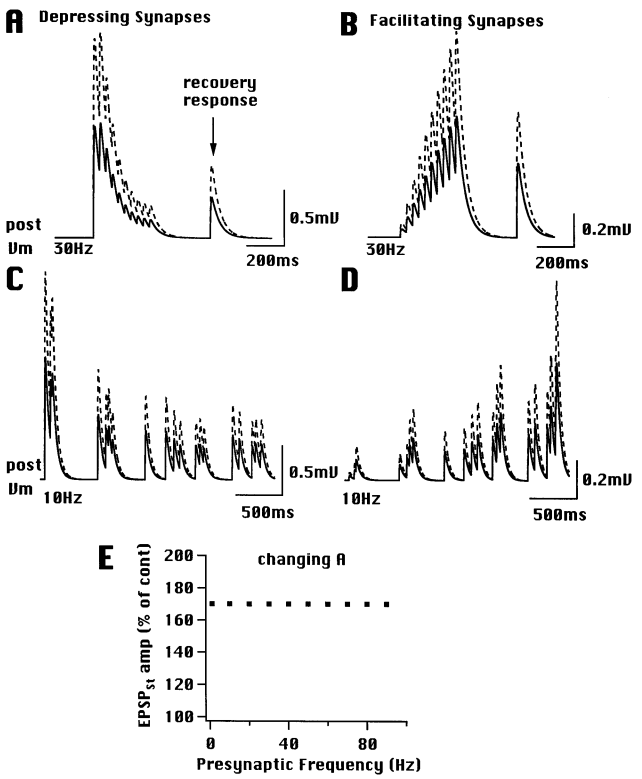

Fig. 5. Phenomenology of changing A. (A) Synaptic responses of depressing synapses when A is increased 1.7-fold. In this simulation, U was 0.4, τ_{rec} was 800 ms and initial A was 1. (B) Synaptic responses of facilitating synapses when A is increased 1.7-fold. In this simulation, U was 0.01, τ_{rec} was 60 ms, τ_{facil} was 3000 ms and initial A was 2. (C,D) Uniform increase in synaptic responses to an irregular train of presynaptic APs at an average frequency of 10 Hz for the depressing synapse (C) and facilitating synapse (D). (E) The change in $EPSP_{St}$ is uniform for all frequencies

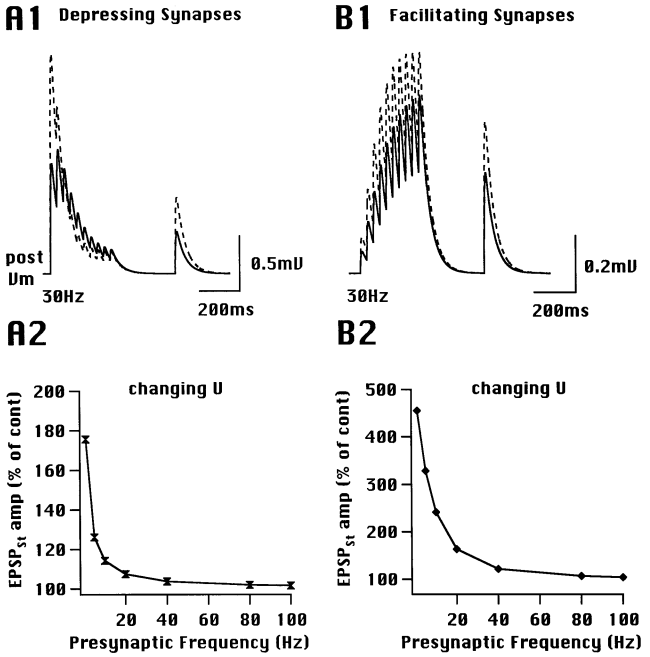

Fig. 6. Phenomenology of changing U. (A1) Synaptic responses of depressing synapses when U was increased from 0.4 to 0.8. In this simulation, A was 1 and τ_{rec} was 800 ms. (A2) Frequency dependence of the effect of changing U in depressing synapses. A was 1 and τ_{rec} was 800 ms and U was increased from 0.4 to 0.8. (B1) Synaptic responses of facilitating synapses when U was increased from 0.1 to 0.05. In this simulation, A was 1, τ_{rec} was 60 ms and τ_{facil} was 3000 ms. (B2) Frequency dependence of the effect of changing U in facilitating synapses. A was 1, τ_{rec} was 60 ms and τ_{facil} was 3000 ms.

a mechanism to selectively regulate low frequency synaptic transmission (Fig. 6). The reason for this is that at high frequencies, Pr either decreases to converge at low values regardless of the initial Pr (presynaptic mechanism of depression) (see Betz, 1970) or Pr becomes irrelevant since recovery from synaptic depression becomes the rate limiting step (postsynaptic mechanism of depression). The convergence of averaged EPSP$_{st}$ at high frequencies starting from two different initial values of Pr has been demonstrated experimentally (Tsodyks and Markram, 1997).

Using the phenomenological model, changing Pr is shown to result in a change in U (termed for example, LTP$_u$ or LTD$_u$) and no change in A, τ_{rec} or t_{facil} (Fig. 6). Changing Pr at facilitating synapses exerts an effect over a broader frequency range since synapses must be driven much harder to reach a point where Pr is sufficiently depressed or where recovery from depression becomes limiting (Fig. 6B2). Phenomenologically, a change in frequency dependence has been referred to as a 'redistribution of synaptic efficacy' since each AP in a train produces a different response while A is kept constant. Redistribution of synaptic efficacy has been observed following Hebbian pairing (Markram and Tsodyks, 1996) and this change reflects a change in U (Tsodyks and Markram, 1997).

We have found that application of cyclothiazide, a blocker of AMPA (L-a-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) receptor desensitization could not block synaptic depression (Markram, 1997), and that blockade of NMDA receptors do not change the kinetics of the depression and that these kinetics are not sensitive to membrane voltage (Markram, 1997) indicating that depression is largely mediated presynaptically at the synaptic connection between neocortical pyramidal neurons. An effect of cyclothiazide on the recovery time from depression was observed, but this could have been due to a presynaptic effect (Bellingham and Walmsley, 1997). For this particular synaptic connection, it therefore appears to be valid to state that coactivity of pre and postsynaptic neurons (Hebbian pairing) induces LTP$_u$ due to a change in Pr.

3.5. Changing depression of synaptic transmission

Previous studies of synaptic plasticity have overlooked the possibility that various conditions could change τ_{rec}. Changing τ_{rec} could constitute a powerful mechanism of regulating synaptic transmission (termed for example, LTP$_d$ and LTD$_d$). The phenomena is expressed as a change in high frequency synaptic transmission (Fig. 7).

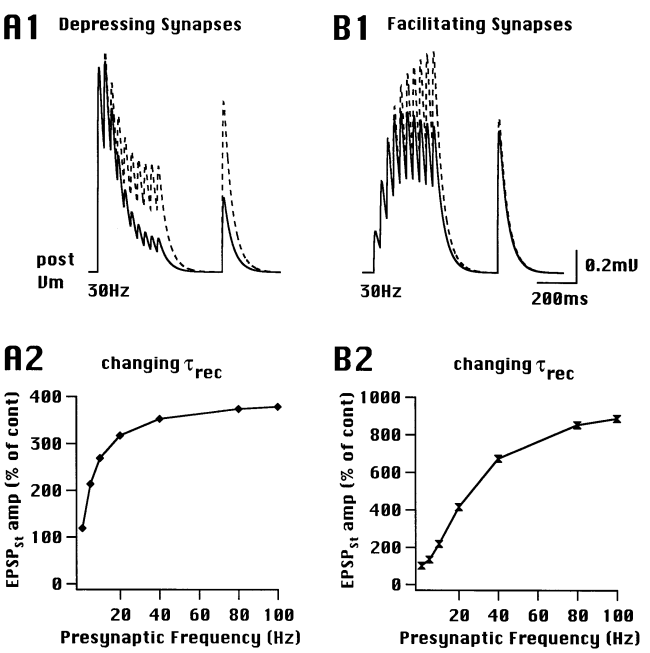

Fig. 7. Phenomenology of changing τ_{rec}. (A1) Synaptic responses of depressing synapses when τ_{rec} was increased from 200 to 800 ms. In this simulation, A was 1 and U was 0.5. (A2) Frequency dependence of the effect of changing τ_{rec} in depressing synapses. A was 1, U was 0.5 and τ_{rec} was increased from 200 to 800 ms. (B1) Synaptic responses of facilitating synapses when τ_{rec} was increased from 60 ms to 600 ms. In this simulation, U was 0.01 and τ_{facil} was 3000 ms. (B2) Frequency dependence of the effect of changing τ_{rec} in depressing synapses. A was 2, U was 0.01, τ_{facil} was 3000 ms and τ_{rec} was increased from 60 to 600 ms.

For facilitating synapses this is particularly important since the significance of any changes are not only determined by the absolute values of U, τ_{rec} and τ_{facil}, but also by their values relative to each other (see below). The biophysical mechanisms responsible for determining τ_{facil} are not completely understood and hence the precise molecular targets for modulation remain to be established.

3.6. Changing facilitation of synaptic transmission

Changes in paired pulse ratios have been used extensively in the pre versus postsynaptic debate for the mechanism of LTP of synaptic strength (see for example, Zalutsky and Nicoll, 1990, Christie and Abraham, 1994, Jung and Larson, 1994, Schulz et al., 1994, Voronin, 1994, Xiang et al., 1994, Hedberg and Stanton, 1995, Schulz et al., 1995, Luthi et al., 1996, Schulz, 1997, Choi and Lovinger, 1997; Torii et al., 1997). There are several problems with this approach: (1) changes in paired pulse ratios actually suggest that the change in transmission is not uniform for all frequencies and hence does not reflect a uniform change in synaptic strength; (2) changes in paired pulse ratios rest on the assumption that frequency dependence is purely presynaptic. While presynaptic mechanisms can clearly determine frequency dependence to a large extent, the precise contribution of pre and postsynaptic factors has not been demonstrated definitively at mammalian CNS synapses; (3) depending on the initial Pr, a jump in Pr could present as a uniform change in paired pulses (see Kullman and Siegelbaum, 1995); (4) presynaptic changes, such as in the size of synaptic vesicles, the neurotransmitter concentration per vesicle or altering the number of vesicles released per postsynaptic receptor cluster could cause uniform changes in paired pulse responses if the postsynaptic receptors are not saturated; (5) particularly in the case of facilitating synapses, it would not be possible to determine that the paired pulse ratio did not change since, for the two first EPSPs, the change could be negligible with a differential change only becoming evident after a series of EPSPs in a train (see for example, Fig. 6(B1); Fig. 7(B1) and Fig. 8(A)). Finally, even if a change in paired pulse ratio is observed and additional statistical data supports a presynaptic origin, then it is still not clear whether Pr or whether depression or facilitation time constants changed.

A change in τ_{facil} results in unique phenomena (termed for example, LTP_f or LTD_f). The phenomena are expressed as a change in transmission only over a selected range of medium frequencies unlike those caused by changing U (low frequencies) or τ_{rec} (high frequencies) (Fig. 8). It has been well established that facilitation has several time constants (see Magleby and Zengel, 1982, Zucker, 1989). It is therefore possible that

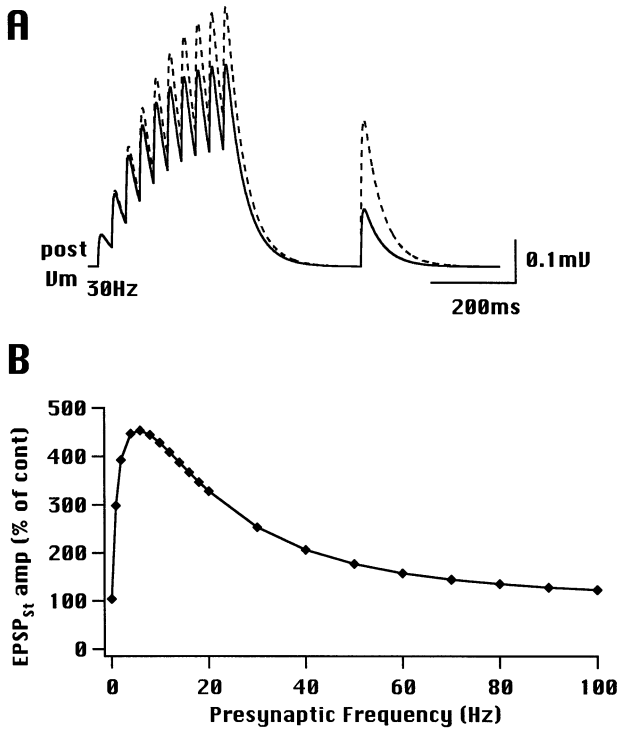

Fig. 8. Phenomenology of changing τ_{facil}. (A) Synaptic response of facilitating synapses when τ_{facil} was increased from 1000 to 3000 ms. A was 2, U was 0.01 and τ_{rec} was 60 ms. (B) Frequency dependence of the effect of changing τ_{facil}. Note that changing τ_{facil} only exerts an effect over an intermediate range of frequencies

both the amplitudes and time constants of multiple components of facilitation could be modulated (see Magleby and Zengel, 1976) producing more selective sub-classes of plasticity phenomena (termed for example, $LTP_{f(n(m))}$ where n would indicate which component of facilitation is affected (1,2...n), and m indicting either the amplitude (a) or time constant, (t)). Each phenomenon could be distinguished using more pointed experiments and more detailed modeling. For paired recordings, the number of experimental trials containing different protocols is usually not enough to obtain accurate sweep averages for many protocols which still makes it difficult to dissect out these potential sub-components. Perforated patch-clamp experiments may help to solve these difficulties.

4. Discussion

By exploring a simple model of frequency-dependent synaptic transmission, we illustrate that there is a potential for multiple synaptic mechanisms, each resulting in a unique phenomena of synaptic plasticity at individual synapses. In line with the short, medium and long-term categorization of different memory processes (see Dudai, 1989) multiple different phenomena of plasticity could occur at single synapses due to changes in each of

the values of A, U, τ_{rec} and $\tau_{facil.}$ Subcomponents of τ_{rec} and τ_{facil} could further amplify the diversity of phenomena. The potential striking differences between the phenomenologies of each synaptic change suggest that frequency-dependent synaptic transmission and plasticity of frequency-dependence are crucial considerations in order to understand the link between synaptic transmission and information processing and the link between synaptic plasticity and learning and memory. Evidence that the various parameters characterizing frequency-dependent synapses can in fact be modulated and the apparent need for multiple interrelated conditions of activity to drive these modifications in a coherent manner, are discussed.

4.1. Heterogeneity of multiple synaptic properties

In a recent study the heterogeneity of the properties of synaptic connections formed by the same axon on different postsynaptic targets was examined (Markram et al., 1998). The results indicate that the connections formed from layer 5 pyramidal neurons onto morphologically similar neurons, differ in the number of putative synapses by as much as 5-fold. For these typically depressing synaptic connections, A differs as much as 20-fold, U as much as 1.45-fold and τ_{rec} up to 3-fold. For any two facilitating synaptic connections converging from two pyramidal neurons of the same morphological class onto a single interneuron, A, differs as much as 4-fold, U as much as 4 fold, τ_{rec} as much as 20-fold and τ_{facil} up to 3-fold. When the same axon contacted a pyramidal neuron and an interneuron, the responses were diametrically opposite with, synaptic depression onto the pyramidal neuron and facilitation onto the interneuron consistent with data from paired recordings (Thomson et al., 1993a,b, Thomson and Deuchars, 1994). These results indicated that the class of frequency dependence is determined by the postsynaptic target (see also Gardner, 1991, Laurent and Sivaramakrishnan, 1992, Davis and Murphey, 1993) and that within a given class of frequency dependence, there exists large heterogeneity in the values of synaptic parameters. This alludes to an enormous 'plastic potential' in which the unique interaction between any two neurons, in the context of network activity, could determine the precise value of each synaptic parameter.

4.2. Redistribution of synaptic efficacy

LTP and LTD have been considered largely in the terms of changing the strength of synapses. This conclusion can not be drawn from experiments examining only low frequency synaptic responses unless the synapses do not display frequency dependence or unless the nervous system ignores high frequency transmission. This 'simplification' has severely constrained the development of concepts of information processing in neural networks and has lead to potentially misconstrued concepts of how synaptic changes relate to learning and memory. Incorporating frequency-dependent synaptic transmission into artificial neural networks reveals that the function of synapses within neural networks is exceedingly more complex than previously imagined (Uziel, A., Tsodyks, M., and Markram H., in preparation). Similarly, plasticity of frequency dependence or redistribution of synaptic efficacy introduces an immense and as yet unexplored richness into how neural network responses may change.

Synaptic heterogeneity is not the only evidence for plasticity of several synaptic parameters: (1) Hebbian pairing of pre and postsynaptic neurons was shown to result in a selective increase in low frequency synaptic transmission (Markram and Tsodyks, 1996) which is due to a specific change in U (Tsodyks and Markram, 1997); (2) while presynaptic regulation of neurotransmitter release is typically considered as a mechanism to block or enhance transmission between neurons, this action rather serves to change the frequency dependence of transmission; (3) paired pulse experiments that demonstrated changes in paired pulse ratios rather demonstrated changes in frequency dependence; (4) we have recently found that an initial stage of LTD_a is preceded by a selective loss of facilitation (LTD_f) (A. Gupta and H. Markram, in preparation); (5) selective changes in both the amplitudes and time constants of sub-components of facilitation that would correspond to $LTP_{f3,a}$, LTD_{f3t} and LTP_{f4t} have been observed at the neuromuscular junction (Magleby and Zengel, 1982).

4.3. Multiple algorithms for synaptic plasticity

How could the nervous system coordinate multiple mechanisms of synaptic plasticity where each results in a different effect on transmission at single synapses and a potentially different effect on information processing within the network? In only a few cases have studies focused specifically on establishing the precise activity conditions that drive synaptic changes. Such studies are essential in order to derive comprehensive algorithms for synaptic plasticity (for review see Fregnac and Shulz, 1994). For the connection between pyramidal neurons, the precise timing of AP discharges of pre and postsynaptic neurons determines whether the EPSP for low frequency stimulation increases or decreases (Markram et al., 1997b). Together with the dependence of the magnitude of the induced change in U on the frequency and number of APs involved in the pairing bursts, an algorithm based on precise spike times has been constructed (Senn et al., 1997).

The conditions that drive changes in A, τ_{rec} and τ_{facil} are not yet clearly established. It seems likely, however,

that while these algorithms would be different, that they would also be interrelated in order to maintain coherency between the individual parameters. This apparent 'need' for interrelated algorithms is indicated by the importance of the relative values of these kinetic parameters in determining the synaptic response i.e. the effect of changing any one parameter depends on the values of the other parameters. For example, the impact of changing τ_{facil} depends on the values of U and τ_{rec} (Fig. 9). It would therefore seem unlikely that the mechanisms which regulate one synaptic parameter would operate independently of the existing value and changes in the other parameters. In other words the different mechanism, phenomena and algorithms for synaptic plasticity at single synapses could be intricately related by a 'code of synaptic plasticity'. An example of interrelated algorithms would be where LTP_u is caused by precise spike times of pre and postsynaptic neurons, while the same conditions in addition to the activation of a metabotropic receptor, would trigger LTP_a. Indeed, activity in the presence of neurotrophins has been shown to result in structural changes (McAllister et al., 1995) and a recent report indicated that two different forms of LTD can be produced with the same stimulation protocol depending on whether a metabotropic receptor is activated or not (Kemp and Bashir, 1997).

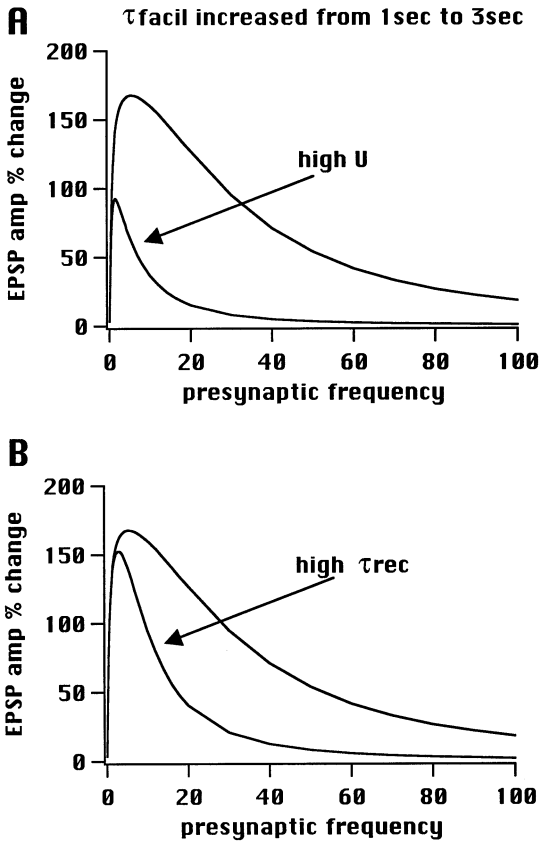

Fig. 9. Impact of changing τ_{facil} depends on τ_{rec} and U values. Simulation of the effect of changing τ_{facil} at different frequencies of presynaptic stimulation. In both (A) and (B) τ_{facil} was increased from 1 to 3 s and the percent change in the steady state EPSP for different frequencies is represented on the y-axis. (A) The impact of changing τ_{facil} is restricted by the value of U. In the control case U was 0.005 and in the 'high U' case, U was 0.1. τ_{rec} and A remained constant at 60 ms and 2 mV (B) The impact of changing τ_{facil} is restricted by the value of τ_{rec}. In the control case, τ_{rec} was 60 ms and in the high τ_{rec} case, τ_{rec} was 600ms. U and A remained constant at 0.005 and 2 mV

An unresolved issue is the generalization of algorithms across different types of synaptic connections. By default it may seem appropriate to assume that there are as many algorithms as there are classes of pre-postsynaptic neurons i.e. potential classes of synapses. Indeed, as mentioned, at least the two broad classes of depressing and facilitating synapses exist and recent evidence suggests that the rules for synaptic modifications are very different at these connections. Repetitive stimulation with brief high frequency bursts (typically used as test pulses) induces LTD_f and LTD_a at facilitating synapses (in preparation) which is not observed at depressing synapses between pyramidal neurons (Markram and Tsodyks, 1996).

5. Conclusion

Experimental evidence indicates that dynamics of neurotransmitter release under different conditions of stimulation are potentially unique for each synapse in an axonal tree. The theoretical analysis presented here indicates that modulation of any one synaptic parameter would produce a distinctive effect on transmission. This approach could be useful in studies of synaptic plasticity not only to characterize the phenomenon that is studied thoroughly and to establish the most likely mechanisms of the change, but also to understand the potential impact of specific modifications on the nervous system and hence may allow a systematic reconstruction of the link between synaptic modifications and learning and memory.

Acknowledgements

This study was supported by an ONR, Minerva, BSF, Grodetsky and Wolfson grants.

References

Amit, D.J., 1989. Modeling Brain Function, Cambridge University Press, New York.

Barnes, C.A., 1995. Involvement of LTP in Memory: Are we 'Searching under the Street Light? Neuron 15, 751–754.

Bashir, Z.I., Alford, S., Davies, S.N., Randall, A.D., Collingridge, G.L., 1991. Long-term potentiation of NMDA receptor-mediated synaptic transmission in the hippocampus. Nature 349, 156–158.

Bellingham, M.C., Walmsley, B., 1997. A presynaptic site of cyclothiazide-sensitive paired pulse depression at a central mammalian glutamatergic synapse. Society for Neurosci Abstracts 145, 11.

Betz, W.J., 1970. Depression of transmitter release at the neuromuscular junction. J Physiol (London) 206, 626–644.

Bliss, T.V.P., Collingridge, G.L., 1993. A synaptic model of memory: Long-term potentiation in the hippocampus. Nature 361, 31–39.

Brodin, L., Löw, P., Gad, H., Gustafsson, J., Pieribone, V.A., Shupliakov, O., 1997. Sustained neurotransmitter release: New molecular clues. European J Neurosci 9, 2503–2511.

Buonomano, D.V., Baxter, D.A., Byrne, J.H., 1990. Small networks of empirically derived adaptive elements simulate some high-order features of classical conditioning. Neural Netw 3, 507–523.

Byrne, J., 1978. Analysis of the synaptic depression contribution to habituation of gill-withdrawal reflex in Aplysia californica. J Neurophysiol 48, 431–438.

Carew, T.J., Walters, E.T., Kandel, E.R., 1981. Classical conditioning in a simple withdrawal reflex in Aplysia californica. J Neurosci 1, 1426–1437.

Castellucci, V., Pinsker, H., Kupfermann, I., Kandel, E.R., 1970. Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in Aplysia. Science 167, 1745–1748.

Ceccarelli, B., Hurlbrut, W.P., 1980. Vesicle hypothesis of the release of quanta of acetylcholine. Physiological revs 60, 396–441.

Choi, S., Lovinger, D.M., 1997. Decreased probability of neurotransmitter release underlies striatal long-term depression and postnatal development of corticostriatal synapses. Proceedings of the National Academy of Sciences (USA) 94, 2665–26670.

Christie, B.R., Abraham, W.C., 1994. Differential regulation of paired-pulse plasticity following LTP in the dentate gyrus. Neuroreport 5, 385–388.

Churchland, P.S., Sejnowski, T.J., 1992. The computational brain. MIT press, Cambridge.

Ciaccia, P., Maio, D., Vacca, G.P., 1992. An analytical short- and long-term memory model of presynaptic plasticity. Biolog Cyber 67, 335–345.

Cruikshank, S.J., Weinberger, N.M., 1996. Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review. Brain Res Rev 22, 191–228.

Davis, G.W., Murphey, R.K., 1993. A role for postsynaptic neurons in determining presynaptic release properties in the cricket CNS: evidence for retrograde control of facilitation. J Neurosci 13, 3827–3838.

del Castillo, J., Katz, B., 1954. Statistical factors involved in the neuromuscular facilitation and depression. J Physiol (London) 124, 574–585.

Dudai, Y., 1989. The Neurobiology of Memory. xford University Press, New York.

Faber, D.S., Korn, H., 1991. Applicability of the coefficient of variation method for analyzing synaptic plasticity. Biophys J 60, 1288–1294.

Feng, T.P., 1941. Studies on the neuromuscular junction. XXVI. The changes of the end-plate potential during and after prolonged stimulation. Chin J Physiol 16, 341–372.

Fregnac, Y., Shulz, D., 1994. Models of synaptic plasticity and cellular analogs of learning in developing and adult visual cortex. In: Casagrande, V.A., Shinkman, P.G. (Eds.), Advances in Neuronal and Behavioral Development, vol. 4. Ablex Publication Corporation, New Jersey, pp. 149–235.

Gardner, D., 1991. Presynaptic transmitter release is specified by postsynaptic neurons of Aplysia buccal ganglia. J Neurophysiol 66, 2150–2154.

Gingrich, K.J., Byrne, J., 1985. Simulation of synaptic depression, posttetanic potentiation, and presynaptic facilitation of synaptic potentials from sensory neurons mediating gill-withdrawal reflex in Aplysia. J Neurophysiol 53, 652–669.

Gluck, M.A., Myers, C.E., 1997. Psychobiological models of hippocampal function in learning and memory. Annu Rev Psychol 48, 481–514.

Hebb, D.O., 1949. The Organization of Behavior. Wiley, New York.

Hedberg, T.G., Stanton, P.K., 1995. Long-term potentiation and depression of synaptic transmission in rat posterior cingulate cortex. Brain Res 670, 181–196.

Hertz, J., Krogh, A., Palmer, R.G., 1991. Introduction to the theory of neural computation. Addison-Wesley, New York.

Hubbard, J.I., 1963. Repetitive stimulation at the neuromuscular junction, and the mobilization of transmitter. J Physiol (London) 169, 641–662.

Hutter, O.F., 1952. Post-tetanic restoration of neuromuscular transmission blocked by d–tubocurarine. J Physiol (London) 118, 216–227.

Jodar, L., Kaneto, H., 1995. Synaptic plasticity: stairway to memory. Jpn J Pharmacol 68, 359–387.

Jonas, P., Racca, C., Sakmann, B., Seeburg, P.H., Monyer, H., 1994. Differences in Ca^{2+} permeability of AMPA-type glutamate receptor channels in neocortical neurons caused by differential GluR-B subunit expression. Neuron 12, 1281–1289.

Jonas, P., Spruston, N., 1994. Mechanisms shaping glutamate-mediated excitatory postsynaptic currents in the CNS. Curr Opin Neurobiol 4, 366–372.

Jones, M.V., Westbrook, G.L., 1996. The impact of receptor desensitization on fast synaptic transmission. Trends Neurosci 19, 96–101.

Jung, M.W., Larson, J., 1994. Further characteristics of long-term potentiation in piriform cortex. Synapse 18, 298–306.

Kauer, J.A., Malenka, R.C., Nicoll, R.A., 1988. A persistent postsynaptic modification mediates long-term potentiation in the hippocampus. Neuron 1, 911–917.

Kemp, N., Bashir, Z.I., 1997. LTD induced by paired pulse low-frequency stimulation in the CA1 region of the adult rat hippocampus in vitro. Society for Neuroscience Abstracts, 679, p. 14.

Klein, M., Shapiro, E., Kandel, E.R., 1980. Synaptic plasticity and the modulation of the Ca^{2+} current. J Exp Biol 89, 117–157.

Korn, H., Sur, C., Charpier, S., Legendre, P., Faber, D.S., 1994. The one-vesicle hypothesis and multivesicular release. Adv Second Messenger Phosphoprotein Res 29, 301–322.

Kullman, D.M., Siegelbaum, S.A., 1995. The site of expression of NMDA receptor-dependent LTP: New Fuel for an old fire. Neuron 15, 997–1002.

Laurent, G., Sivaramakrishnan, A., 1992. Single local interneurons in the locust make central synapses with different properties of transmitter release on distinct postsynaptic neurons. J Neurosci 12, 2370–2380.

Liao, D., Hessler, N.A., Malinow, R., 1995. Activation of postsynaptic silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature 375, 400–404.

Liley, A.W., 1956. The quantal components of the mammalian end-plate potential. J Physiol (London) 133, 571–587.

Liley, A.W., North, K.A.K., 1953. An electrical investigation of the effects of repetitive stimulation on mammalian neuromuscular junction. J Neurophysiol 16, 509–527.

Luthi, A., Mohajeri, H., Schachner, M., Laurent, J.P., 1996. Reduction of hippocampal long-term potentiation in transgenic mice ectopically expressing the neural cell adhesion molecule L1 in astrocytes. J Neurosci Res 46, 1–6.

Magleby, K.L., Zengel, J.E., 1976. Long term changes in augmentation, potentiation, and depression of transmitter release as a function of repeated synaptic activity at the frog neuromuscular junction. J Physiol (London) 257, 471–494.

Magleby, K.L., Zengel, J.E., 1982. A quantitative description of stimulation-induced changes in transmitter release at the frog neuromuscular junction. J Gen Physiol 80, 613–638.

Maren, S., Baudry, M., 1995. Properties and mechanisms of Long-Term synaptic plasticity in the Mammalian Brain: Relationships to Learning and Memeory. Neurobiol Learning Mem 63, 1–18.

Markram, H., Tsodyks, M., 1996. Redistribution of synaptic efficacy between neocortical pyramidal neurons. Nature 382, 807–810.

Markram, H., 1997. A network of Tufted Layer 5 Pyramidal Neurons. Cereb Cortex 7, 523–533.

Markram, H., Lübke, J., Frotscher, M., Roth, A., Sakmann, B., 1997a. Physiology and anatomy of synaptically coupled connections between thick tufted pyramidal neurons in the developing rat neocortex. J Physiol (London) 500, 409–440.

Markram, H., Lübke, J., Frotscher, M., Roth, A., Sakmann, B., 1997b. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275, 213–215.

Markram, H., Wang, Y., Tsodyks, M., 1998. Differential synaptic signaling via the same axon of neocortical pyramidal neurons. Proceedings of the National Academy of Science (USA), vol. 95, pp. 5323–5328.

McAllister, A.K., Lo, D.C., Katz, L.C., 1995. Neurotrophins regulate dendritic growth in developing visual cortex. Neuron 15, 791–803.

McEachern, J.C., Shaw, C.A., 1996. An alternative to the LTP orthodoxy: a plasticity-pathology continuum model. Brain Res Rev 22, 51–92.

McNaughton, B.L., 1982. Long–term synaptic enhancement and short-term potentiation in rat fascia dentata act through different mechanisms. J Physiol (London) 324, 249–262.

Morris, R.G.M., Kandel, E.R., Squire, L., 1988. The Neuroscience of learning and memory: cells, neural circuits and behavior. Trends Neurosci 11, 125–127.

Murthy, V.N., Sejnowski, T.J., Stevens, C.F., 1997. Heterogeneous release properties of visualized individual hippocampal synapses. Neuron 18, 599–612.

Pinsker, H., Kandel, E.R., Castellucci, V., Kupfermann, I., 1970. An analysis of habituation and dishabituation in Aplysia. Adv Biochem Psychopharmacol 2, 351–373.

Schulz, P.E., 1997. Long-term potentiation involves increases in the probability of neurotransmitter release. Proceedings of the National Academy of Science (USA) 94, 5888–5893.

Schulz, P.E., Cook, E.P., Johnston, D., 1994. Changes in paired-pulse facilitation suggest presynaptic involvement in long-term potentiation. J Neurosci 14, 5325–5337.

Schulz, P.E., Cook, E.P., Johnston, D., 1995. Using paired-pulse facilitation to probe the mechanisms for long-term potentiation (LTP). J Physiol (Paris) 89, 3–9.

Senn, W., Tsodyks, M., Markram, H., 1997. An algorithm for synaptic plasticity based on exact timing of pre- and post-synaptic action potentials. Lect Notes Comput Sci 1327, 121–126.

Siegelbaum, S.A., Kandel, E.R., 1991. Learning-related synaptic plasticity: LTP and LTD. Curr Opin Neurobiol 1, 113–120.

Softky, W.R., Koch, C., 1993. The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. J Neurosci 13, 334–350.

Stevens, C.F., 1993. Quantal release of neurotransmitter and long-term potentiation. Neuron 10, 55–63.

Sutton, R.S., Barto, A.G., 1990. Toward a modern theory of adaptive networks: expectation and prediction. Psychol Rev 88, 135–170.

Takeuchi, A., 1958. The long lasting depression in neuromuscular transmission of frog. Jpn J Physiol 8, 102–113.

Teyler, T.J., Discenna, P., 1984. Long–term potentiation as a candidate mnemonic device. Brain Res 319, 15–28.

Teyler, T.J., Fountain, S.B., 1987. Neuronal plasticity in the mammalian brain: relevance to behavioral learning and memory. Child Dev 58, 698–712.

Thies, R.E., 1965. Neuromuscular depression and the apparent depletion of transmitter in mammalian muscle. J Neurophysiol 212, 431–446.

Thomson, A.M., Deuchars, J., 1994. Temporal and spatial properties of local circuits in neocortex. Trends in Neurosci 17, 119–126.

Thomson, A.M., Deuchars, J., West, D.C., 1993a. Large, deep layer pyramid-pyramid single axon EPSPs in slices of rat motor cortex display paired pulse and frequency-dependent depression, mediated presynaptically and self-facilitation, mediated postsynaptically. J Neurophysiol 70, 2354–2369.

Thomson, A.M., Deuchars, J., West, D.C., 1993b. Single axon excitatory postsynaptic potentials in neocortical interneurons exhibit pronounced paired pulse facilitation. Neurosci 54, 347–360.

Tong, G., Jahr, C.E., 1994. Multivesicular release from excitatory synapses of cultured hippocampal neurons. Neuron 12, 51–59.

Torii, N., Tsumoto, T., Uno, L., Astrelin, A.V., Voronin, L.L., 1997. Quantal analysis suggests presynaptic involvement in expression of neocortical short- and long-term depression. Neurosci 79, 317–321.

Tsodyks, M., Markram, H., 1997. The Neural Code between Neocortical Pyramidal Neurons Depends on Neurotransmitter Release Probability. Proceedings of the National Academy of Sciences (U.S.A) 94, 719–723.

Voronin, L.L., 1994. Quantal analysis of hippocampal long-term potentiation. Rev Neurosci 5, 141–170.

Xiang, Z., Greenwood, A.C., Kairiss, E.W., Brown, T.H., 1994. Quantal mechanism of long-term potentiation in hippocampal mossy-fiber synapses. J Neurophysiol 71, 2552–2556.

Xie, X., Liaw, J.S., Baudry, M., Berger, T.W., 1997. Novel expression mechanism for synaptic potentiation: alignment of presynaptic release site and postsynaptic receptor. Proceedings of the National Academy of Science (USA) 94, 6983–6988.

Zalutsky, R.A., Nicoll, R.A., 1990. Comparison of two forms of long-term potentiation in single hippocampal neurons. Science 248, 1619–1624.

Zucker, R.S., 1989. Short-term synaptic plasticity. Annu Rev Neurosci 12, 13–31.