Synaptic depression: a dynamic regulator of synaptic communication with varied functional roles

The past 20 years have witnessed something of a revolution in our understanding of synaptic transmission and its regulation. Synaptic transmission is no longer viewed as being mediated by static processes of fixed strength but rather by dynamic ones that are continuously regulated on many time scales. Although most recent studies have focused on slower regulation (time scales >1 s), such as long-term potentiation and depression, it is well known that synaptic transmission can also be modulated transiently (<1 s). A well-studied example is post-tetanic potentiation, the transient increase in synaptic efficacy that accompanies high-frequency stimulation of presynaptic axons[1–3]. At any particular synapse the effects of prior stimulation on the postsynaptic response depend on the balance between facilitation and depression, which can occur simultaneously at some synapses. For example, in the connection between group Ia muscle-spindle afferents and motoneurons in the adult cat, facilitation and potentiation predominate over a low-frequency depression[2]. By contrast, the same class of synapse exhibits depression at even modest repetition rates during development in rat and chick – a property that has been attributed to immaturity of the transmitter-releasing machinery[4–6].

Synaptic depression is not unique to developing synapses. It can be a primary form of synaptic modulation at some vertebrate cortical synapses[7–9]. In fact, depression can be exhibited by pyramidal cells projecting to other pyramidal cells whereas pyramidal inputs to interneurons can potentiate[10–12]. The function of this depression is unknown but several new studies have shed light on its role. This work suggests that synaptic depression can endow networks with novel and unexpected dynamic properties[9,13–16].

Release probability affects the transient but not steady response

Markram and Tsodyks[9,16] used simultaneous whole-cell recordings from synaptically-connected pyramidal cells of rat neocortical slices to investigate the roles of potentiation and depression in synaptic communication (basic features are summarized in Fig. 1A). They induced a form of long-term potentiation in the connection by a period of paired intracellular stimulation of the pre- and postsynaptic cells. Then they examined the effects of this facilitation on successive excitatory postsynaptic potential (EPSP) amplitudes produced by a train of action potentials generated by brief stimuli applied to the presynaptic cell. In control recordings, before the pairing, the leading action potential often failed to elicit an EPSP and subsequent EPSPs tended to decrease in amplitude.

The pairing procedure decreased the number of failures following the first action potential and increased the amplitude of the train's first EPSP (compared with the unfacilitated control case), presumably by increasing release probability. Surprisingly, however, the depressed, steady-state EPSP level reached during the train was not enhanced by the conditioning, unless the test train's frequency was low (<20–30 Hz). Moreover, pairing accelerated the rate of approach to the steady state, that is, pairing increased the rate of synaptic depression. Similar results were found with other manipulations that enhance release probability, such as increasing extracellular calcium concentration[16]. Consistent with these results, it has been shown in other parts of the nervous system that decreasing the probability of transmitter release can abolish synaptic depression in a train[5,16–17] or in a paired-pulse protocol[18].

Collectively, these results show that alterations in EPSP amplitude based on single impulses (equivalent to the leading one of a train) do not necessarily imply a functional change in efficacy during a (high-frequency) train of stimuli. This might be particularly important when considering long-term potentiation (LTP), which is

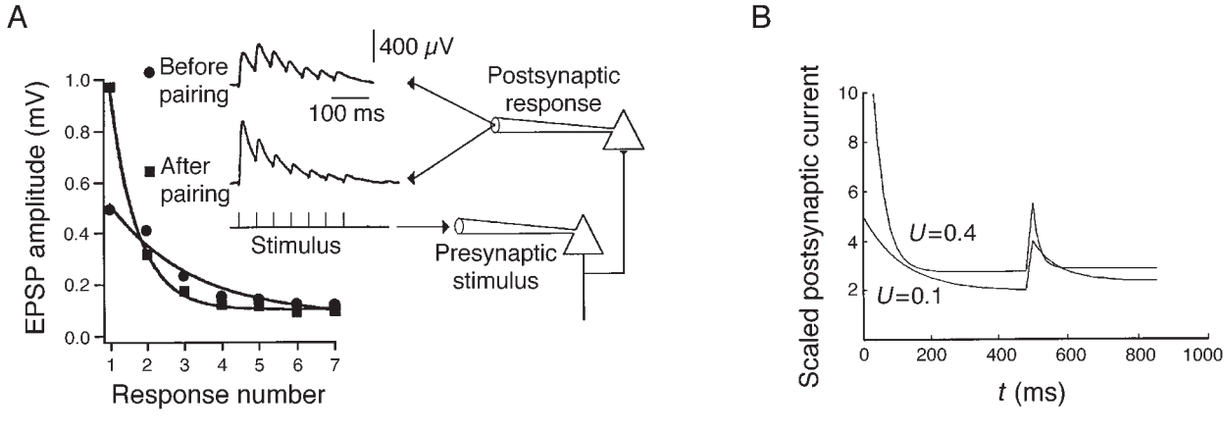
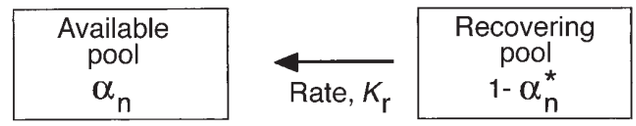


Fig. 1. ***Examples of synaptic depression in the connections between two pyramidal cells in the rat neocortex.*** *The cells were recorded simultaneously. The control recordings (before pairing) show the postsynaptic responses of one cell following stimulation of the other.* **(A)** *The graph illustrates the progressive decrease in the amplitude of successive excitatory postsynaptic potentials (EPSPs) in the train. The responses after pairing were obtained following a period of conjoint intracellular stimulation (see text for details) which probably increased the amount of transmitter release and thereby the rate of synaptic depression (square symbols on graph).* Figure modified from Markram and Tsodyks[9]. **(B)** *Curves computed with the model illustrated in Box 1, assuming an afferent population with input rate of 50 Hz that changes to 100 Hz (at* t *= 450 ms) showing the transient increase in postsynaptic response [summed excitatory postsynaptic currents (EPSCs)],* U* α* *input frequency. Note that the steady-state responses just before and after the transient are similar. The upper curve (*U *= 0.4) shows a more rapid decay, as has been found experimentally when* U *is increased by pairing* (A)*. The lower curve (*U *= 0.1) shows the slower decay of scaled postsynaptic current when* U *is reduced.*

Michael J. O'Donovan and John Rinzel
Section on Developmental Neurobiology, Laboratory of Neural Control, NINDS and Mathematical Research Branch, NIDDK, National Institutes of Health, Bethesda, MD 20892, USA.

 0166 - 2236/97/$17.00 PII: S0166-2236(97)01124-7

Box 1. Discrete-time model



$$\alpha_n \xrightarrow{n\text{th spike}} \alpha_n - U\alpha_n = (1-U)\,\alpha_n = \alpha_n^*$$

In the next time interval (between the nth and (n+1)th spike) the available pool recovers by an amount: $K_r\,T\,(1-\alpha_n^*)$ so that

$$\alpha_{n+1} = \alpha_n^* + K_r T\,(1-\alpha_n^*)$$

$$\alpha_{n+1} = (1-U)\,\alpha_n + K_r T\,[1-(1-U)\,\alpha_n]$$

At steady state, $\alpha_n \longrightarrow \alpha_{ss}$:

$$\alpha_{ss} = \frac{K_r T}{U + (1-U)K_r T} \doteq \frac{K_r T}{U}$$

Fig. ***Discrete-time model for the dynamics of the transmitter pool; relative pool size just prior to the nth spike is*** α_n. *This description[13,16] is a valid approximation for small* $K_r T$. *The final expression for* α_{ss} *also assumes small* $K_r T$.

assessed traditionally by single shock stimulation. In this light, synaptic depression might be considered a form of dynamic feedback that maintains synaptic efficacy (averaged over afferents and time) approximately constant in the face of changes in the probability of transmitter release. However, while providing this stability, synaptic depression can enhance the transient response of a network to sudden changes in afferent firing, as described below.

A minimal model for synaptic depression

Box 1 summarizes, for high-frequency inputs, an elegantly simple model[13,16] that accounts quantitatively for many aspects of synaptic depression. Suppose that each action potential utilizes a fraction U of the available transmitter (or, more generally, the available resource pool), α_{ss}. Thus, if U increases, the leading EPSPs will be potentiated but the depression will proceed more quickly. Eventually, for a steady input train, the response adapts to a steady level. Now suppose that after each spike the released transmitter enters a recovery pool from which resources are returned (with recovery rate K_r) to the pool which is available for release. At steady state, the amount recovered in the time T between inputs (frequency, $1/T$) just balances the per spike usage: $U\alpha_{ss} = K_r T$. This simple approximate formula shows that the postsynaptic response at steady state is proportional to $K_r T$ and thus is independent of U (see model output in Fig. 1B), just as determined experimentally (Fig. 1A). It also shows that the available pool size decreases inversely with input rate. Tsodyks and Markram[16,19] note that this inverse dependence on frequency applies for inputs that exceed a limiting rate, K_r/U. At low frequencies the recovery is fast enough to replenish the pool available for release before the next action potential. From the model one further concludes that the depression at high rates is compensated for by the linear summation of inputs arriving at frequency $1/T$ (that is, $1/T \times K_r T$), predicting that the steady response is independent of input rate.

Depression favors temporal encoding over rate encoding

Some consequences of this lack of frequency sensitivity were also explored by Abbott and colleagues[13] in a recent experimental and modeling study of synaptic depression in slices of rat primary visual cortex. They suggest that synaptic depression may serve as a form of cortical gain control by depressing the postsynaptic responses to rapidly-firing afferents. In their model and experiments, high-frequency stimulation of afferent inputs results in a progressive decline in EPSP amplitude until a steady state is reached that is approximately independent of frequency. Under such conditions the postsynaptic neuron loses information about the steady-state firing frequency of the afferents. However, the authors show that this loss of rate-encoding ability is accompanied by an increase in the temporal sensitivity of the network, or the postsynaptic cell, to a sudden change in presynaptic firing rates (as illustrated in the model in Fig. 1B). As described by Tsodyks and Markram[16], who also saw this, synaptic depression endows the system with the ability to detect synchronous rate changes in a population of afferents. Abbott *et al.*[13] found that the induced postsynaptic conductance transient is proportional to the fractional change in the afferents' firing rate. As a consequence, the postsynaptic cell can detect sudden rate changes in the low- and high-frequency afferents with about equal sensitivity. Networks comprised of such synapses become phasically sensitive to rate fluctuations of the low-frequency afferents that would otherwise be swamped by the EPSPs originating from more rapidly firing inputs.

Synaptic depression as a rhythmogenic mechanism

A quite different effect of synaptic depression is seen in networks of cultured neurons and in the isolated spinal cord. In both preparations it has been proposed that activity-dependent synaptic depression plays an important role in the genesis of periodic, spontaneous activity[14,15]. Senn and colleagues[14] developed a computational network model that predicts the spontaneous activity (population bursting with periods of seconds) generated by networks of cultured spinal neurons. The highly idealized model embodies purely excitatory connections that are uniformly distributed in space. The model has two variables – one describing the average firing frequency and one describing the slower-evolving activity-dependent synaptic depression. Maintained oscillations arise as follows. Recurrent excitation causes autocatalytic growth in population activity which is then quenched by the slow negative feedback of synaptic depression. During periods of low activity, depression recovers and the network becomes increasingly excitable until a point is reached where it can fire again, thereby initiating another phase of synaptic depression.

A similar argument has been used to account for the occurrence of spontaneous activity in the isolated spinal cord of the chick embryo[15]. This preparation generates periodic episodes of rhythmic bursting that recur on the time scale of minutes. During an episode spinal neurons fire several bursts and then stop. The burst frequencies are similar to those

described by Senn and colleagues[14]. It has been proposed that discharge in a cycle is limited by a short-term synaptic depression, although several alternative mechanisms could contribute[15]. A similar mechanism could regulate the occurrence of episodes but in a much longer time scale[15]. We have recently modeled this behavior minimally using a three-variable, continuous time model with two distinct synaptic depression variables, one of which is ultra slow[20]. The existence of slow and even slower components of synaptic depression has also been observed in excitatory synapses of the rat visual cortex, although in this system the slowest component has a time constant of seconds (Ref. 17 and J.A. Varela, W. Sen, J. Gibson, J. Fost, L.F. Abbott and P.B. Nelson, unpublished observations) rather than minutes as proposed for spinal networks[15].

How does it work and so what?

It appears that a bewildering array of processes can contribute to the mechanism of synaptic depression. Markram and Tsodyks argued that the depression they observed in cortical cells was probably dependent on the amount of transmitter released, as indicated in the model (Fig. 1), although changes in the affinity of postsynaptic glutamate receptors could not be excluded[9]. However, in studies of the visual cortex several postsynaptic factors have been eliminated because synaptic depression at excitatory synapses is unaffected by postsynaptic receptor blockade with the non-NMDA receptor antagonist CNQX or by reduction of receptor desensitization by cyclohexemide (J.A. Varela *et al.*, unpublished observations). In developing muscle afferent–motoneuron contacts a presynaptic mechanism for depression has also been implicated because depression is abolished when transmitter release is decreased by low extracellular Ca^{2+} concentrations or bath-application of the $GABA_B$ agonist, baclofen[5]. In cultured spinal cord neurons transmitter depletion is probably also responsible for synaptic depression at some synapses. However, at other synapses in such cultures, the depression might be due to failure of the presynaptic action potential to invade all of the terminals[6]. It has also been proposed that synaptic depression might be caused by a form of negative feedback. This can occur if excess transmitter leaks from synaptic sites to engage presynaptic autoreceptors which decrease transmitter release[8,21], or by an activity-dependent reduction in the presynaptic calcium currents responsible for transmitter release[22]. Finally, alterations in the sensitivity of postsynaptic receptors have also been implicated in synaptic depression[23].

It should be clear from this review that synaptic depression has the potential to be an important contributor to the properties and function of networks. But are these interesting properties actually engaged in active networks? This will be a difficult question to answer because it will require modifying the degree of synaptic depression within a network and documenting the effects on the network output. This may be easier to accomplish in rhythmically active networks whose output can be easily measured. It will be considerably more difficult to establish whether or not synaptic depression actually enhances the dynamic sensitivity of networks, both for experimental reasons and because we do not know how such information is actually used in functioning networks.

Finally, it will be important in future studies to establish whether synaptic depression is actively regulated by the nervous system and whether or not its effects can be modified by events in the postsynaptic cell. For example, it is possible that active conductances in dendrites might be capable of compensating or modifying the effects of depression at some synapses.

Perhaps many different classes of synapse can express both depression and facilitation. Certainly, there is evidence that both processes can be co-expressed at the same synapse. Can the nervous system control the relative expression of either process at individual synapses? Is synaptic depression a property that is regulated retrogradely by the postsynaptic cell, as has been proposed for developing synapses in the spinal cord[25]?

References

1 **Curtis, D.R. and Eccles, J.C.** (1960) *J. Physiol.* 150, 374–398
2 **Lev-Tov, A., Pinter, M.J. and Burke, R.E.** (1983) *J. Neurophysiol.* 50, 379–398
3 **Feng, T.P. and Li, T.H.** (1941) *Chin. J. Physiol.* 16, 37–50
4 **Lee, M.T. and O'Donovan, M.J.** (1991) *J. Neurosci.* 11, 2564–2573
5 **Lev-Tov, A. and Pinco, M.** (1992) *J. Physiol.* 447, 149–169
6 **Streit, J., Luscher, C. and Luscher, H-R.** (1992) *J. Neurophysiol.* 68, 1793–1803
7 **Thomson, A.M. and Deuchars, J.** (1994) *Trends Neurosci.* 17, 119–126
8 **Deisz, R.A. and Prince, D.A.** (1989) *J. Physiol.* 412, 513–541
9 **Markram, H. and Tsodyks, M.** (1996) *Nature* 882, 807–810
10 **Thomson, A.M., Deuchars, J. and West, D.C.** (1993) *Neuroscience* 54, 347–360
11 **Thomson, A.M.** (1997) *Science* 275, 179–180
12 **Thomson, A.M. and Deuchars, J.** *J.Physiol.* (in press)
13 **Abbott, L.F. *et al.*** (1997) *Science* 275, 220–224
14 **Senn, W. *et al.*** (1996) *Neural Networks* 9, 575–588
15 **O'Donovan, M.J. and Chub, N.** (1997) *Semin. Cell Dev. Biol.* 8, 21–28
16 **Tsodyks, M. and Markram, H.** (1997) *Proc. Natl. Acad. Sci. U. S. A.* 94, 719–723
17 **Nelson, S.B. *et al.*** (1996) *Soc. Neurosci. Abstr.* 22, 952
18 **Thomson, A.M., Deuchars, J. and West, D.C.** (1993) *J. Neurophysiol.* 2354–2369
19 **Tsodyks, M.V. and Markram, H.** (1996) in *Lecture Notes in Comp. Sci.* (von der Malsburg, C. *et al.*, eds), 1112, pp. 445–450, Springer-Verlag
20 **Rinzel, J. and O'Donovan, M.J.** (1997) *Abstract for CNS*97 meeting*
21 **Scanziani, M. *et al.*** (1997) *Nature* 385, 630–634
22 **Jia, M. and Nelson, P.G.** (1986) *J. Neurophysiol.* 56, 1257–1267
23 **Numann, R.E. and Wong, R.K.** (1984) *Neurosci. Lett.* 47, 289–294
24 **Seebach, B.S. and Mendell, L.M.** (1996) *J. Neurophysiol.* 76, 3875–3885

OBITUARY

John Zachary Young (1907–1997)

Patrick D. Wall
Dept of Physiology, St Thomas' Hospital Medical School, Lambeth Palace Road, London, UK SE1 7EH.

By happenstance, three men stood next to each other in the line to matriculate into Oxford University in 1925: Derek Denny-Brown, Jack Eccles and J.Z. Young. Each was to have a considerable impact, in their way, on the neuroscience of this century. Denny-Brown, the oldest, had been an ANZAC soldier and came as a Rhodes Scholar from New Zealand to work with Sherrington and was to concentrate on the cerebrum and motor systems. Eccles, a Rhodes Scholar from Australia, also came to join Sherrington and was to force his order on spinal cord and cerebellum[1]. Young, fresh from Marlborough School, was to explore freely the relation of brain and behaviour. Together in their interest in the nervous system, their characters could not have been more different. Denny-Brown was a suave introvert, Eccles rough and aggressive while J.Z. Young was bacchanalian and dionysian.

J.Z. Young was born in Bristol to a Quaker family. While we all know that

 0166 - 2236/97/$17.00 PII: S0166-2236(97)01161-2