Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation

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In many brain areas, including the cerebellar cortex, neocortex, hippocampus, striatum and nucleus accumbens, brief activation of an excitatory pathway can produce long-term depression (LTD) of synaptic transmission. In most preparations, induction of LTD has been shown to require a minimum level of postsynaptic depolarization and a rise in the intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ in the postsynaptic neurone. Thus, induction conditions resemble those described for the initiation of associative long-term potentiation (LTP). However, data from structures susceptible to both LTD and LTP suggest that a stronger depolarization and a greater increase in $[Ca^{2+}]_i$ are required to induce LTP than to initiate LTD. The source of Ca^{2+} appears to be less critical for the differential induction of LTP and LTD than the amplitude of the Ca^{2+} surge, since the activation of voltage- and ligand-gated Ca^{2+} conductances as well as the release from intracellular stores have all been shown to contribute to both LTD and LTP induction. LTD is induceable even at inactive synapses if $[Ca^{2+}]_i$ is raised to the appropriate level by antidromic or heterosynaptic activation, or by raising the extracellular Ca^{2+} concentration $[Ca^{2+}]_o$. These conditions suggest a rule (called here the ABS rule) for activity-dependent synaptic modifications that differs from the classical Hebb rule and that can account for both homosynaptic LTD and LTP as well as for heterosynaptic competition and associativity.

Use-dependent long-term changes in synaptic efficacy are thought to form a basis for learning and memory. Since the discovery of long-term potentiation (LTP) in the hippocampus[1], use-dependent enhancement of synaptic transmission has been observed in a large number of brain structures. In the majority of cases, induction of LTP is input specific and associative; that is, modifications are restricted to the activated inputs, and synapses are potentiated only if they are active while the respective postsynaptic dendrite is sufficiently depolarized (for review see Ref. 2).

More recently, evidence has been obtained that synaptic transmission can also undergo long-term depression (LTD). The time constants for the development and maintenance of LTD resemble those of LTP, although LTD (in contrast to LTP) has been observed to occur both at active and inactive synapses. When LTD occurs at inputs whose activation contributes to the induction of the modification, it is called 'homosynaptic' LTD (Fig. 1A–C). When it manifests itself at inputs that had been inactive during induction, it is addressed as 'heterosynaptic' (Fig. 1D).

Some experimental protocols result in a depression of synaptic transmission that has a shorter duration (5–20 min) than LTD[3]. In analogy with short-term potentiation, this more transient change can be referred to as short-term depression (STD). The fact that STD can be elicited even when LTD is blocked[4–7] suggests that STD and LTD may depend on different mechanisms. Therefore, a discussion of STD is not included in this review.

Mechanisms of induction of homosynaptic LTD

The stimulation protocols used for the induction of homosynaptic LTD differ in different structures of the CNS. In the neocortex[4,8,9], the striatum[10] and the nucleus accumbens[11], homosynaptic LTD (Fig. 1A) can be induced by high-frequency tetanic stimuli that resemble those suitable for the induction of LTP. By contrast, in CA1 of the hippocampus[6,7,12,13] low-frequency stimulation (1–15 Hz) is more effective in inducing LTD, especially if maintained over prolonged periods of time (10–15 min)[6,7]. Short low-frequency tetani induce LTD only if applied in alternation with a high-frequency stimulation of a second input converging on the same neurones[14–16] (Fig. 1B). In the cerebellum LTD is obtained only if different inputs are activated in conjunction[17–21] (Fig. 1C): transmission between parallel fibres and Purkinje cells becomes depressed when parallel fibres are coactivated with climbing fibres converging onto the same Purkinje cells.

Despite the fact that the stimulation protocols suitable for LTD induction differ in various brain structures, the induction mechanisms share common features. Induction of homosynaptic LTD appears to require a minimum depolarization of the postsynaptic neurone because it is blocked if the postsynaptic cell is hyperpolarized by current injection during application of stimuli that would normally have induced LTD. This has been shown in cultures[21] and slices[22] of the cerebellum and in slices of the visual cortex[4], the hippocampus[7] and the striatum[10]. Accordingly, homosynaptic LTD has been obtained in the neocortex by weak stimuli that would have been ineffective when applied alone, but that are effective when paired with postsynaptic depolarizing pulses[23]. In the cerebellum, the activation of climbing fibres that is normally required for the induction of LTD in parallel fibres (see above) can be substituted by direct depolarization of Purkinje cells[22,24,25], suggesting that the coactivation of climbing fibres only is required to induce a sufficiently strong depolarization of Purkinje cells during the period when parallel fibres are active. The fact that in some experimental protocols hippocampal LTD can be induced only when the postsynaptic cell is hyperpolarized during low-frequency (5–10 Hz) tetanic stimulation[14,26] is not inconsistent with the conclusion that LTD induction requires a critical level of postsynaptic depolarization; in this particular case injecting hyperpolarizing currents appears to be necessary to maintain depolarization within the range suitable for LTD induction (see below).

Another common feature of the processes leading to LTD is their dependency on the intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ in the postsynaptic neurone. In

all structures investigated so far, LTD induction is blocked if intracellular Ca^{2+} is buffered by injection of the Ca^{2+}-chelators 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetra-acetic acid (BAPTA) or ethyleneglycol-bis-(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA) (Fig. 2). This has been shown for the cerebellum[27], the neocortex[5,28] and the hippocampus[7]. Evidence that LTD induction actually requires a surge of $[Ca^{2+}]_i$ above the normal resting level comes from two observations. (1) In slices of the visual cortex, increasing the extracellular Ca^{2+} concentration $[Ca^{2+}]_o$ to 4 mM makes it possible to induce LTD with weak tetani that would have been ineffective otherwise[29]. (2) In cultured Purkinje cells, reduction of $[Ca^{2+}]_o$ to zero prevents the depression of responses to iontophoretically applied glutamate that would normally occur when these cells are strongly depolarized in the presence of glutamate[25].

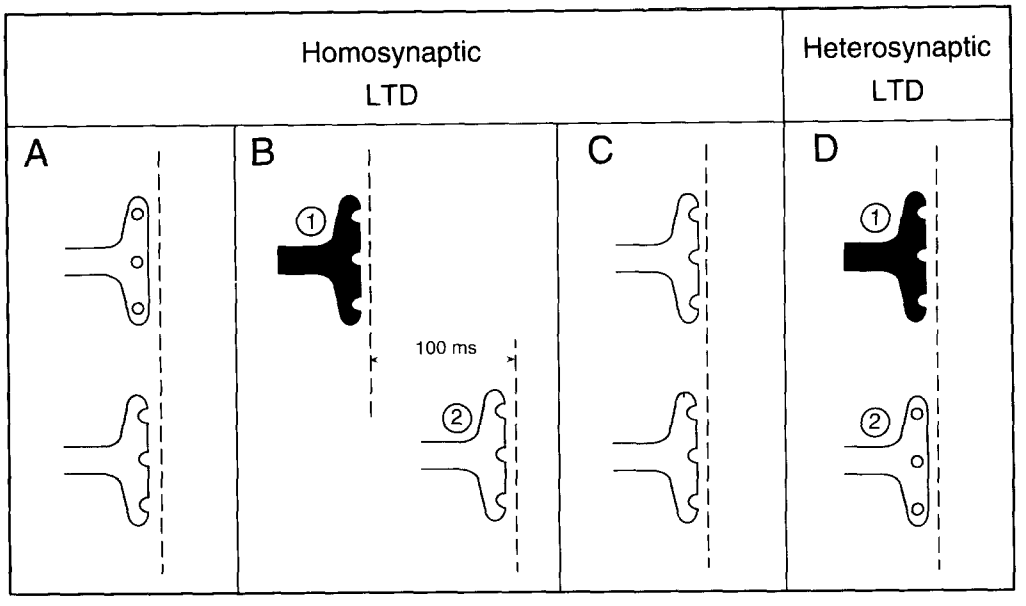

Fig. 1. *Conditions of synaptic activation leading to homosynaptic and heterosynaptic long-term depression (LTD). The homosynaptic category includes cases where activation of the input undergoing modification contributes to the induction of the change but would alone not have been sufficient. Three conditions have been described for the induction of homosynaptic LTD.* **(A)** *Activation of one input system (grey synapse) alone is sufficient to induce LTD. This induction protocol has been found effective in neocortex[4,8,9], hippocampus[6,7], striatum[10] and nucleus accumbens[11]. Except in the hippocampus, the stimulation parameters suitable for LTD induction resemble those required for the induction of long-term potentiation (LTP) (10–50 Hz trains that are 2–3 s long and are repeated 3–5 times). However, in CA1 low-frequency stimulation (1–15 Hz) was found to be more effective, especially if maintained over prolonged periods of time (10–15 min)[6,7].* **(B)** *An input system (2) undergoes LTD only if it is activated in alternation with a second, conditioning (1) input (black synapse). This induction protocol has been effective in areas CA1 (Ref. 14) and CA3 (Ref. 15) of the hippocampus and the dentate gyrus[16]. Typically, the pathway undergoing LTD is activated with single shocks, while the conditioning input is stimulated with brief (50 ms), high-frequency (100 Hz) trains repeated at intervals of 200 ms (theta burst stimulation). This protocol not only induces LTD of the test input (2) but also LTP of the conditioning input (1).* **(C)** *An input system undergoes LTD when it is activated in conjunction with a second input (white synapse). This is the case in the cerebellum where coactivation of climbing fibres and parallel fibres leads to LTD of synapses between parallel fibres and Purkinje cells[17–21]. The frequency and duration of effective stimuli are in the range of 4 Hz and 0.5–2 min, respectively.* **(D)** *Heterosynaptic LTD. An input system (2) undergoes LTD even when inactive if other inputs (1) to the same cell are strongly activated. This form of LTD has been observed in the hippocampus[12,63–69] and neocortex (Ref. 70 and Artola, A. and Singer, W., unpublished observations). The induction protocols require strong postsynaptic activation and hence high-frequency stimulation of input (1). Accordingly, this input often undergoes LTP when heterosynaptic LTD is induced[63] (but see Refs 66, 68 and Artola, A. and Singer, W., unpublished observations).*

Relationship between the induction of homosynaptic LTD and associative LTP

The conditions for the induction of homosynaptic LTD, postsynaptic depolarization and an increase in $[Ca^{2+}]_i$ within the postsynaptic dendrite qualitatively resemble those required for the induction of associative LTP (see review in Ref. 2). However, there is an important quantitative difference: induction of LTP requires a stronger postsynaptic depolarization than induction of LTD. This was first shown in the visual cortex where LTD and LTP can be induced one after the other in the same pathway using the same stimulation parameters but maintaining different levels of postsynaptic depolarization by current injection during tetanic stimulation[4]. A high-intensity tetanus that is alone sufficient to induce LTD can induce LTP when paired with depolarizing current injection, and causes no long-term synaptic modification when paired with hyperpolarizing current injection.

The notion that LTP induction requires stronger postsynaptic depolarization than the induction of LTD is also supported by the results of experiments in which the level of postsynaptic depolarization sustained during tetanic stimulation was manipulated pharmacologically. In slices of the visual cortex, a low-intensity tetanus – which alone induces no long-term change of synaptic gain – leads to LTD when cells are disinhibited with 0.1–0.2 μM of the $GABA_A$ antagonist bicuculline, and LTP when the concentration of bicuculline is raised to 0.3 μM (Ref. 4). Likewise, LTD is induced if *N*-methyl-D-aspartate (NMDA) receptors are blocked (thus reducing the depolarizing response to the tetanus) under stimulation conditions that would normally induce LTP (0.3 μM bicuculline)[4]. These results have led to the notion that there is one voltage-dependent threshold for the induction of LTD and another threshold distinct for the induction of LTP (Fig. 3A). If the first threshold (known as Θ^-) is reached, the activated synapses depress, and if the second threshold (called Θ^+) is reached, which requires stronger depolarization, the activated synapses potentiate. Accordingly, there are two ranges of membrane potential (E_m) within which synapses do not undergo long-term modifications: (1) when E_m remains below the threshold for LTD (Θ^-); and (2) when E_m is around the second threshold (Θ^+), which separates the two ranges of E_m that lead to LTD and subsequently to LTP.

Evidence is now available that these two thresholds apply also to use-dependent synaptic modifications in other brain areas such as the prefrontal cortex, the striatum and the hippocampus. In slices of the

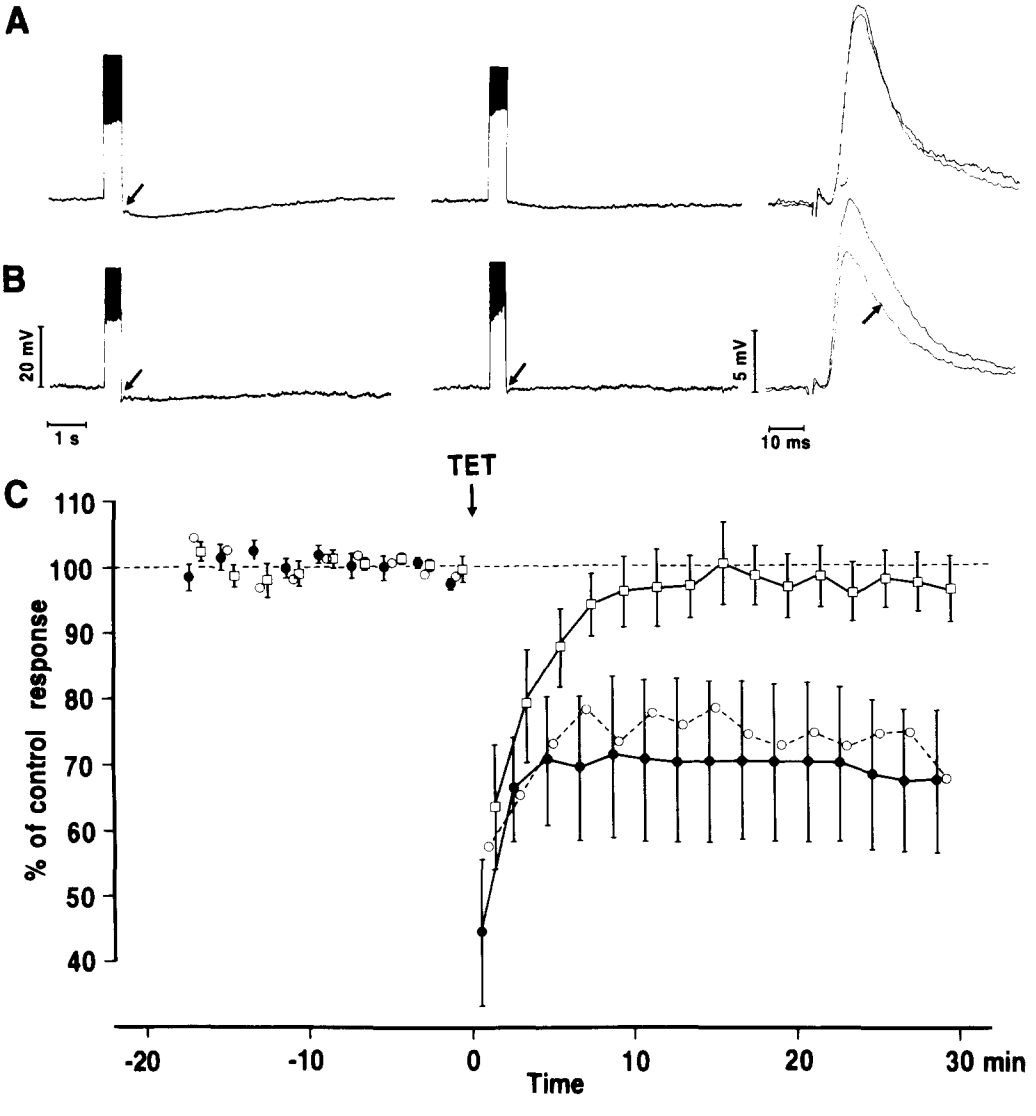

Fig. 2. *Effect of intracellular injection of BAPTA on the induction of long-term depression (LTD) in rat visual cortex.* **(A,B)** *The left and middle diagrams of (A) and (B) show responses to brief (500 ms) depolarizing current pulses [+0.7 nA in (A) and +0.8 nA in (B)] before (left) and after (middle) BAPTA injection. In the cell tested in (A) blockade of early afterhyperpolarizing potentials (AHPs) is complete except for the slow Ca^{2+}-independent AHP. Comparison of postsynaptic potentials recorded before and 20 min after the tetanus shows no evidence of LTD (A, right). In the cell in (B), BAPTA injection has been interrupted before complete disappearance of the fast, Ca^{2+}-dependent AHP [arrow in (B, middle)]. Comparison of postsynaptic potentials (B, right) recorded before and 20 min after (arrow) tetanus reveals that LTD could still be elicited in this cell. For the AHP measurements in (A) and (B), cells were depolarized to (A) −49 and (B) −50 mV by current injection. [Membrane potential E_m was −79 mV in (A) and −81 mV in (B).]* **(C)** *Time-course of post-tetanic changes in the amplitude of postsynaptic potentials elicited from white matter in controls cells (●; n=4) and in cells injected with BAPTA (□; n=5). Open circles refer to the cell shown in (B). Stimulus intensity during tetanus (TET) was ten times the threshold intensity (18.0 ± 2.0 V in control cells and 16.3 ± 1.4 V in injected cells; mean ± SEM). (From Ref. 5.)*

prefrontal cortex a tetanic stimulus that would normally elicit LTP induces LTD when the depolarizing response to the tetanus is reduced by blocking NMDA receptors with Mg^{2+} (Ref. 30). In the striatum the same tetanic stimulus, which normally produces LTP in Mg^{2+}-free medium, induces LTD in the presence of extracellular Mg^{2+} at a concentration $[Mg^{2+}]_o$ of 1.2 mM and no modification when the postsynaptic cell is hyperpolarized during the conditioning tetanus in the presence of 1.2 mM $[Mg^{2+}]_o$[10,31]. Low $[Mg^{2+}]_o$ favours the opening of NMDA-receptor-gated Ca^{2+} channels[32,33] and enhances the depolarizing response to the tetanus. Thus, the induction of LTD and LTP in the striatum shows the same voltage dependence that is observed in the visual cortex. In area CA1 of the hippocampus, low-frequency (around 1 Hz) stimulation induces LTD while high-frequency stimulation (>10 Hz) induces LTP[6,12]. Likewise, the effect of a tetanus of a given frequency can be modified by current injection. A tetanus induced by a stimulation frequency of 5 Hz has no long-term effect on synaptic transmission by itself, probably because this frequency is intermediate between the frequencies suitable for the induction of LTD and LTP[6,12], giving a postsynaptic depolarization around the Θ^+ threshold. However, this same tetanus induces LTD when paired with hyperpolarizing current injection and LTP when paired with depolarizing current injection[14]. Similarly, low-frequency tetani (1–15 Hz) that normally induce LTD (see above) are no longer effective if cells are hyperpolarized during stimulation[7]. These observations are all compatible with the hypothesis that the induction mechanisms of LTD and LTP have different thresholds that are both related to postsynaptic depolarization.

Recently, it has been demonstrated in neocortex and in hippocampus that not only α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)- but also NMDA-receptor-mediated synaptic transmission can undergo both LTD and LTP[26,34–37]: these modifications also appear to have different thresholds for induction. When AMPA receptors are blocked in area CA1, a 10 Hz tetanus, which alone has no long-term effect (see above), induces LTD of the NMDA-receptor-mediated EPSP if paired with hyperpolarizing current injection and LTP when paired with depolarizing current injection[26]. Results pointing in the same direction have been obtained in experiments in which LTP and LTD were induced by pairing individual NMDA-receptor-mediated EPSPs, elicited at a frequency of 1 Hz, with depolarizing pulses of different amplitude. Weak depolarizing pulses led to LTD, while stronger pulses produced LTP[37].

The data reviewed so far indicate that induction of both LTD and LTP require an increase in $[Ca^{2+}]_i$ and that LTP is induced at more depolarized levels of E_m than LTD. It is possible that different levels of postsynaptic depolarization favour the activation of different Ca^{2+} sources, such as voltage-gated Ca^{2+} channels, NMDA-receptor-gated channels and metabotropic glutamate (mGlu) receptors, and that the source of Ca^{2+} determines the direction of the

synaptic change. Another possibility is that strong depolarization leads to more pronounced increases in $[Ca^{2+}]_i$ than weak depolarization and that the induction of LTP requires a greater increase in $[Ca^{2+}]_i$ than the induction of LTD[38].

Early evidence favoured the first hypothesis as it suggested that Ca^{2+} entering through NMDA-receptor-gated channels mediates the induction of LTP[39,40], while Ca^{2+} liberated from intracellular stores following activation of mGlu receptors leads to LTD. This view equated the LTP threshold Θ^+ with the activation threshold of NMDA-receptor-gated Ca^{2+} conductances[41]. Since a critical level of postsynaptic depolarization is needed to reduce the Mg^{2+} block of the NMDA-receptor-gated channel[32,33], this interpretation accounted well for the fact that LTP induction requires strong postsynaptic depolarization. The evidence that in the hippocampus, neocortex and striatum blockade of NMDA receptors prevents the induction of LTP[39,40] but not of LTD[4,14,30,31] (but see below), and the fact that cerebellar Purkinje cells, which are not susceptible to associative LTP, lack NMDA receptors[42,43] altogether appeared compatible with this view. Moreover, evidence has been obtained that activation of mGlu receptors facilitates LTD induction. In cultured Purkinje cells[25], in cerebellar wedges[44] and in slices of area CA1 (Stanton, P., pers. commun.), combined application of AMPA and 1-aminocyclopentane-1s,3R dicarboxylic acid (1s,3R-ACPD, an agonist of the mGlu receptors) induces a persistent desensitization of AMPA receptors. Recently, it has been reported that even activation of mGlu receptors alone can lead to LTD[45]. Conversely, blockade of mGlu receptors by the antagonist 2-amino-3-phosphonopropionate (AP3) can prevent the induction of LTD in the hippocampus[46], neocortex (Crépel, F., pers. commun., and Artola, A., unpublished observations) and cultured Purkinje cells[25]; however, because the receptor specificity of AP3 is low definite conclusions cannot be made from these results.

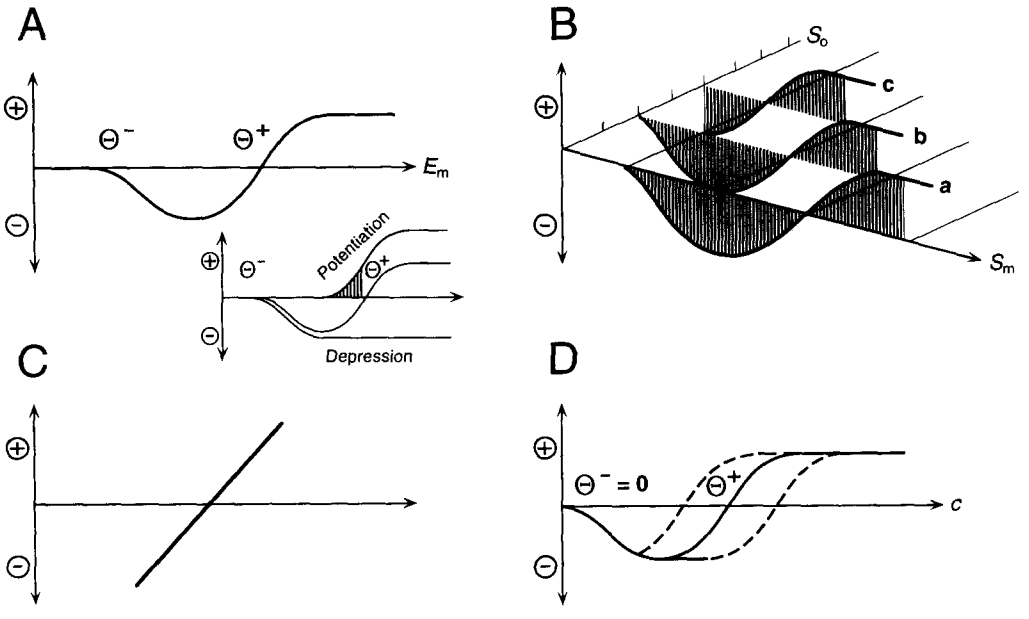

Fig. 3. *A summary of synaptic modification rules.* **(A)** *The ABS ('Artola, Bröcher and Singer') rule: the direction of the synaptic gain change depends on the membrane potential (E_m) of the postsynaptic cell, or in more mechanistic terms, on the amplitude of the surge of intracellular Ca^{2+} concentration $[Ca^{2+}]_i$. If the first threshold Θ^- is reached, a mechanism is activated that leads to long-term depression (LTD); if the second threshold Θ^+ is reached, another process is triggered that leads to long-term potentiation (LTP)* **(inset)**. *Since the ABS rule permits synaptic changes to occur at inputs that are themselves inactive, it can account for both homosynaptic and heterosynaptic modifications. In addition, the existence of Θ^- implies that if postsynaptic depolarization remains below this threshold, then the gain of synapses remains unchanged, irrespective of whether they are active or inactive.* **(B)** *The 'extended' ABS rule: the relationship between the direction of synaptic modifications and the activation of the modified input (S_m) is a function of the activation of other inputs (S_o). Increasing the activity of input S_o leads to a gradual leftward shift of the function describing the relationship between activation of input S_m and the resulting modification of S_m. Note that condition (a) is similar to that shown in (A).* **(C)** *The covariance rule[82]: the synaptic gain change is a linear function of postsynaptic activity that crosses the x axis at a positive value (Θ^+). Depending on how the postsynaptic activity compares with this threshold, Θ^+, either LTD or LTP will be induced.* **(D)** *The BCM ('Bienenstock, Cooper and Munro') rule[83]: the direction of the synaptic gain change is a scalar function Φ(c) of postsynaptic activity c, which is defined as the product between presynaptic activity and synaptic efficacy. Thus, synapses need to be active to undergo a modification. The function Φ(c) changes sign at a particular value of c, called the modification threshold Θm. For $c<\Theta m$, Φ(c) is negative and active synapses depress; for $c>\Theta m$, Φ(c) becomes positive and active synapses potentiate. Θm is thus similar to Θ^+ in the ABS rule. The BCM rule also includes a threshold similar to Θ^-, but in contrast to the ABS rule this threshold membrane potential occurs when c=0. This implies that, for any value of $c<\Theta^+$, synaptic strength decays until it reaches 0, where it stabilizes. An additional important feature of the BCM rule is that the value of Θ^+ is not fixed but instead increases according to a non-linear function with the average output of the cell.*

Data have gradually become available that are no longer compatible with the view that LTP and LTD induction depend selectively on activation of NMDA and mGlu receptors, respectively. There is now clear evidence that LTP can be induced without the activation of NMDA receptors. Under certain conditions, such as stimulation at very high frequencies[47] or blockade of K^+ channels[48], associative LTP can be induced in hippocampal area CA1 after blockade of NMDA receptors. Likewise, LTP independent of NMDA receptors has been obtained in the visual cortex of young rats and kittens[49]. These induction conditions all produce a very strong postsynaptic depolarization and presumably a massive Ca^{2+} entry through voltage-gated Ca^{2+} channels[47,50], thus suggesting a role of these channels in LTP induction. The lack of a clear relationship between the activation of different glutamate receptors and the induction of LTD and LTP is further documented by recent data indicating that in hippocampal area CA1[51,52] and in the dorsolateral septal nucleus[53] mGlu receptors are involved in LTP induction, and that in both the hippocampus[6,7] and the visual cortex[54] activation of NMDA-receptor-gated Ca^{2+} conductances can contribute to LTD induction. Finally, there is evidence that activation of voltage-gated Ca^{2+} channels can also contribute to the induction of LTD. In the cerebellum, activation of parallel fibres[22] or bath application of

1s,3R-ACPD[55] induces LTD of synapses between parallel fibres and Purkinje cells if Purkinje cells are also depolarized by current injection that is likely to activate voltage-gated Ca^{2+} channels. Thus, there is no stringent correlation between the activation of particular glutamate receptors or Ca^{2+} sources and the induction of LTP and LTD.

Most of the available data are compatible with the hypothesis that the sign of the synaptic modification could depend on the amplitude of the $[Ca^{2+}]_i$ surge – the induction of LTP requiring a greater surge of $[Ca^{2+}]_i$ than the induction of LTD. Experiments in hippocampal slices indicate that a rise in $[Ca^{2+}]_i$ is necessary to induce LTP[56] and that an increase in $[Ca^{2+}]_i$ may alone be sufficient to trigger the potentiation of synaptic transmission[57]. A similar dependence on $[Ca^{2+}]_i$ has recently been demonstrated for the induction of LTD in slices of both the hippocampus and the rat visual cortex. In area CA1, depression of synaptic transmission was induced by strongly depolarizing the postsynaptic neurone, either with antidromic activation[58–60] or current injection[60]. This depression depends on Ca^{2+} entry because it is blocked if $[Ca^{2+}]_o$ is low[60], but it is independent of the activation of glutamate receptors because it remains induceable if synaptic transmission is blocked during stimulation. Similarly, in slices of the visual cortex, LTD can be induced in the absence of evoked synaptic activation by raising $[Ca^{2+}]_o$ transiently to 4 mM. This Ca^{2+}-induced LTD depends on postsynaptic E_m because it is only obtained in cells with a E_m that is less negative than −79 mV, and because it can be prevented by hyperpolarizing the postsynaptic neurone during bath application of high $[Ca^{2+}]_o$[29]. This indicates that the depression is caused by a postsynaptic Ca^{2+}-dependent process and is not due to direct effects of high $[Ca^{2+}]_o$ on presynaptic release.

The following observations suggest that the induction of LTP requires a larger increase in $[Ca^{2+}]_i$ than the induction of LTD. (1) In the neocortex, incomplete buffering of intracellular Ca^{2+} by EGTA or BAPTA readily prevents the induction of LTP but still permits the induction of LTD[5,61,62] (Fig. 2). (2) In area CA1 of the hippocampus, a 20 Hz tetanus normally induces LTP but when $[Ca^{2+}]_o$ is lowered from 2.5 to 0.5 mM this tetanus leads to LTD[7]. (3) The requirements for $[Ca^{2+}]_i$ changes account well for the different voltage-dependent thresholds of LTP and LTD as the influx of Ca^{2+} through NMDA-receptor-gated and voltage-gated Ca^{2+} channels increases with depolarization. (4) This agrees with the notion that coactivation of NMDA receptors favours LTP induction since NMDA receptor activation leads to a particularly strong surge of Ca^{2+} in the dendritic spine. (5) It is compatible with the evidence that any source of Ca^{2+} can contribute to either LTP or LTD induction, and that the critical determinants are the stimulation protocols – with activation conditions that cause greater increases of $[Ca^{2+}]_i$ being more likely to induce LTP than LTD (see above).

Heterosynaptic LTD

So far we have considered only homosynaptic LTD; that is, where activity in the modified pathway contributed to its modification. However, if all that is needed for LTD to occur is an appropriate surge of $[Ca^{2+}]_i$ in the respective postsynaptic profile, all conditions causing a sufficient increase of $[Ca^{2+}]_i$ should lead to LTD, irrespective of whether the synapses undergoing depression are active or inactive. Several observations indicate that this is indeed the case. There is evidence from the hippocampus[12,63–69] and the neocortex (Ref. 70 and Artola, A. and Singer, W., unpublished observations) that tetanic stimulation of one excitatory input can cause depression of another, non-stimulated excitatory input to the same neurone (heterosynaptic LTD) (Fig. 1D). This heterosynaptically induced LTD can be prevented by blocking voltage-gated Ca^{2+} channels[71,72] and is facilitated by application of BAY-K864458, an agonist of L-type Ca^{2+} channels[73], suggesting that it is triggered by Ca^{2+} entry in a similar manner to homosynaptically induced LTD.

For the induction of heterosynaptic LTD a signal has to spread from the site of activation to the synapses that undergo depression [see Fig. 4, especially part (D)]. This signal could consist of passively or actively propagating depolarization, which then activates voltage-gated Ca^{2+} channels in the vicinity of the synapses that become depressed[74], or it could consist of propagating Ca^{2+} waves. Several observations suggest that synaptic activation has to cause strong postsynaptic depolarization in order to produce heterosynaptic depression: (1) induction of heterosynaptic LTD requires high frequency stimulation; (2) it is facilitated by reducing GABAergic inhibition (Refs 68, 69, 73 and Artola, A. and Singer, W., unpublished observations); and (3) it is usually prevented by blockade of NMDA receptors (Refs 73, 75 and Artola, A. and Singer, W., unpublished observations; see also Ref. 69). Activation of NMDA receptors is probably necessary to reach the required level of depolarization but it is also possible that it acts by contributing directly to the increase of $[Ca^{2+}]_i$.

Heterosynaptic LTD is not input specific. However, it can be inferred from its dependency on strong postsynaptic depolarization that it will be more easily induced in synapses close to those that have been activated[67].

Because the induction of heterosynaptic LTD requires strong postsynaptic activation, stimulus conditions suitable for the induction of heterosynaptic LTD can induce LTP of the stimulated afferents[63] (Fig. 1D and Fig. 4D); however, the two processes are not causally related. Heterosynaptic LTD can be induced in the absence of homosynaptic LTP (Refs 66, 68 and Artola, A. and Singer, W., unpublished observations) and vice versa.

The Ca^{2+} hypothesis

The data summarized in this review suggest: (1) a rise in $[Ca^{2+}]_i$ is necessary to trigger both LTD and LTP; (2) the increase in $[Ca^{2+}]_i$ required to induce LTP has to be significantly larger than that necessary for LTD induction; and (3) the amplitude of the $[Ca^{2+}]_i$ increase rather than the source of Ca^{2+} appears to be the relevant variable for the induction of synaptic modifications. Thus, it is possible to relate the two voltage-dependent thresholds for LTD and LTP to corresponding changes in $[Ca^{2+}]_i$. This is essentially what Lisman[38] has postulated. According to his model, a moderate rise in $[Ca^{2+}]_i$ should lead to a predominant activation of phosphatases, while a

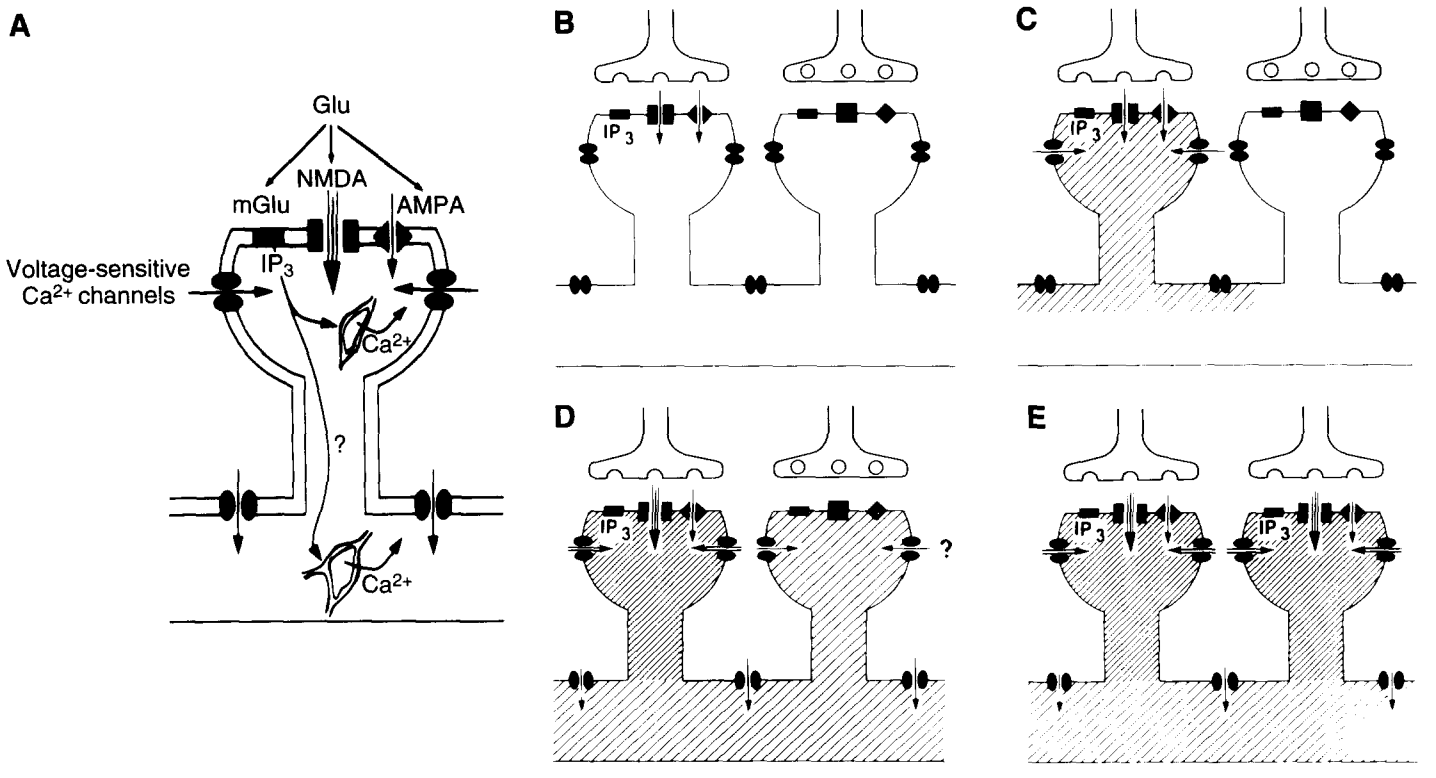

Fig. 4. *The suggested role of the intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ in use-dependent synaptic modifications.* **(A)** *Summary of ligand-gated and voltage-gated mechanisms that modulate $[Ca^{2+}]$ in the postsynaptic dendritic compartment.* **(B–E)** *Homosynaptic and heterosynaptic modifications of synaptic transmission for two inputs terminating on spines of the same dendritic segment. Mechanisms influencing $[Ca^{2+}]_i$ are indicated by the same symbols as in (A). Arrows indicate Ca^{2+} movements and their number indicates the amplitude of the flux. The density of the hatching reflects the expected increase of $[Ca^{2+}]_i$. In (B), (C) and (D) only the left-hand input is active, while in (E) both inputs are simultaneously active. The four conditions also differ in the amplitude of the depolarizing responses of the postsynaptic dendrite. It is assumed that this amplitude is determined both by the activity of the modifiable synapses and by the state of the many other excitatory, inhibitory and modulatory inputs to the same dendritic compartment (not shown).* **(B)** *α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), N-methyl-D-aspartate (NMDA) and metabotropic glutamate (mGlu) receptors are only moderately activated; voltage-gated Ca^{2+} conductances are inactive. There is no substantial rise in $[Ca^{2+}]_i$ and no lasting modification of synaptic transmission at the active synapse.* **(C)** *In addition to the conditions in (B), voltage-gated Ca^{2+} conductances are also activated. $[Ca^{2+}]_i$ rises to an intermediate level and leads to long-term depression (LTD) of the active synapses. There is only a small spread of depolarization and Ca^{2+} from the active spine to other dendritic compartments.* **(D)** *The depolarizing response is assumed to be stronger than in (C); accordingly, NMDA-receptor-gated and voltage-gated Ca^{2+} conductances are also more activated. The massive increase of $[Ca^{2+}]_i$ in the activated spine leads to long-term potentiation (LTP). Moreover, depolarization spreads to other compartments of the dendrite where it activates voltage-gated conductances. This is assumed to lead to an intermediate rise in $[Ca^{2+}]_i$ at the postsynaptic side of the inactive synapse, which as a result undergoes heterosynaptic depression.* **(E)** *Conditions are as in (D) except that the second input is now also active. This facilitates the recruitment of ligand-gated Ca^{2+} sources at the synapses of the second input and raises $[Ca^{2+}]_i$ above threshold Θ^+ (see Fig. 3) so that the second input is no longer depressed but undergoes LTP. Because the first input already causes substantial depolarization of the postsynaptic compartment, the second input can undergo LTP at activation levels well below those that would be required if the first input had not been activated. Thus, the ABS rule (see Fig. 3) accounts not only for homosynaptic LTD and LTP, from which it has been derived originally, but also for heterosynaptic competition and association.*

stronger increase would favour activation of kinases. This proposal is compatible with the recent evidence that the efficacy of glutamate-receptor-gated ion channels can be altered in opposing ways by dephosphorylation and phosphorylation[76,77].

It follows that it should not matter whether the depolarization required for Ca^{2+} entry is caused by the activity of the very synapses that are going to be modified (S_m) or by that of other synaptic inputs (S_o). Thus, the relationship between the direction of the synaptic gain changes and postsynaptic depolarization (Fig. 3A) can be extended to heterosynaptic modifications. The consequences of this generalization are examined in Fig. 3B. The effect of increasing the activity of inputs S_o is a gradual shift to the left of the curve describing the relationship between activation of input S_m and the resulting modifications of S_m. As S_o increases, less and less activation of S_m is required to reach the thresholds for LTD (Θ^-) and LTP (Θ^+) at S_m [curve (b)] and eventually threshold Θ^- will be reached at synapses S_m even if they are not active themselves [curve (c)]; that is, heterosynaptic depression occurs. It follows further that under the conditions described in curve (c) concomitant activation of S_m should prevent input S_m from undergoing heterosynaptic depression if this activation is sufficient to reach threshold Θ^+ at the synapses of S_m. So far, these predictions are all in accord with experimental data. Finally, very strong activation of inputs S_o should shift the curve so far to the left that synapses S_m undergo LTP even if they are inactive. However, with the commonly used activation protocols, this heterosynaptic form of LTP has not been observed (but see Ref. 68). Probably, activation of voltage-gated Ca^{2+} channels or propagating Ca^{2+} waves are alone not sufficient to raise $[Ca^{2+}]_i$ above

threshold Θ^+. Available evidence suggests that under the usual stimulation conditions Θ^+ can only be reached if ligand-gated processes are also activated – this activation being caused by the input S_m itself. This agrees with the evidence that activation of NMDA-receptor-gated Ca^{2+} channels is much more effective in raising Ca^{2+} within dendritic spines[78,79] than activation of voltage-gated Ca^{2+} channels. Thus, ligand-gated Ca^{2+} sources such as the NMDA receptor and perhaps also the mGlu receptor allow inputs to reach threshold Θ^+, which is required to potentiate synapses or to protect them against heterosynaptic LTD.

Our proposal of how both homosynaptic and heterosynaptic modifications depend on membrane potential (E_m) and the activation of various Ca^{2+} sources is summarized in Fig. 4.

Synaptic modification rules

The analysis of use-dependent synaptic modifications in the visual cortex *in vitro* has led to the formulation of a synaptic modification rule, referred to as the ABS rule[80], which differs substantially from the classical Hebb rule[81] in that it includes a negative term. On theoretical grounds Sejnowski[82] (Fig. 3C) and Bienenstock, Cooper and Munro[83] (hence the 'BCM' rule) (Fig. 3D) have postulated biphasic synaptic modification rules that resemble those identified *in vitro* because they also contain a negative term. As summarized in the legend to Fig. 3, similarities prevail between the theoretical postulates and experimental results but there are also some differences. The experimental data suggest that the only control parameter determining synaptic modifications is postsynaptic depolarization or, in more mechanistic terms, the amplitude of the postsynaptic $[Ca^{2+}]_i$ surge. Hence, the ABS rule permits synaptic changes to occur at inputs that are themselves inactive and therefore includes also the rules that have been formulated to account for activity-dependent synaptic competition between converging afferents[84,85]. The BCM rule has been developed to account for experience-dependent modifications of synaptic connections in the developing visual cortex, while the ABS rule has been derived from data obtained in the mature cortex where changes in connectivity do no longer occur. Since the BCM rule accounts very well for most of the published developmental data[86], there is an attractive possibility that the induction mechanisms leading to experience-dependent modifications of connectivity during early development are similar to those mediating use-dependent changes of synaptic gain such as LTD and LTP in the mature cortex (for a more detailed discussion of this possibility see Ref. 87).

Concluding remarks

Attributing a pivotal role to changes in $[Ca^{2+}]_i$ in triggering use-dependent synaptic modifications should not distract from the importance of the processes that precede and follow the surge of $[Ca^{2+}]_i$. It is to be expected that these, too, determine probabilities and thresholds of synaptic modifications to a crucial extent. Thus, modulatory synaptic inputs such as cholinergic and catecholaminergic projections can be expected to influence substantially the probabilities with which a given input pattern reaches LTD and LTP thresholds, since such inputs modify excitability and thereby influence Ca^{2+} entry. For example, combined application of noradrenergic and cholinergic agonists lowers considerably the threshold for LTP induction[88]. Likewise, it is conceivable that a $[Ca^{2+}]_i$ surge of a given amplitude has different effects on synaptic gain changes, depending on the state of the many modulatory inputs that can directly influence it via G-protein-coupled receptors and second messenger cascades downstream of the Ca^{2+} signal.

It is also possible that the mechanisms required for the manifestation of LTP and LTD are not expressed to the same extent in all the cells. Thus, different cells or even different synapses on the same cell are likely to differ with respect to the probability with which a particular increase in $[Ca^{2+}]_i$ triggers LTP or LTD. It appears rather unlikely, for example, that the sole reason for the non-induceability of LTP in the cerebellum is an insufficient increase in $[Ca^{2+}]_i$. Although Purkinje cells lack NMDA receptors, influx of Ca^{2+} through voltage-gated Ca^{2+} channels and release from intracellular stores has been shown to cause very substantial increases in $[Ca^{2+}]_i$[89,90]. It might still be argued that Ca^{2+} from these sources does not reach the concentration required for LTP at sites where this is required but the possibility should not be dismissed that Purkinje cells lack mechanisms required for LTP induction altogether (e.g. certain Ca^{2+}-activated enzyme systems).

All these factors will influence the shape and the position of the function depicted in Fig. 3B. Hence, under natural activation conditions, changes in synaptic gain can be expected to depend not only on the activity in the processing circuits proper but also critically on the many other factors that control the depolarization of dendritic compartments, the amplitude of $[Ca^{2+}]_i$ changes and the signalling cascades that are activated by the increase in $[Ca^{2+}]_i$.

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