REVIEW

Synaptic plasticity, metaplasticity and bcm theory

Jedlicka P

*Institute of Pathophysiology, Medical Faculty, Comenius University, Bratislava, Slovakia.***peterjedlicka@yahoo.com**

Abstract

In many regions of the brain, the activity-dependent changes in synaptic strength depend on the frequency and timing of presynaptic stimulation and postsynaptic activity (synaptic plasticity), as well as the history of activity at those synapses (metaplasticity). The Bienenstock, Cooper and Munro (BCM) theory made several assumptions about how synapses modify and these have helped to guide various neurobiological and neurocomputational experiments. There does appear to be a good correspondence of the synaptic plasticity and metaplasticity experimental data with the BCM model. ***(Fig. 1, Ref. 57.)***
Key words: synaptic plasticity, metaplasticity, BCM, synaptic modification threshold, spike timing, Hebbian synapse, NMDA receptor, AMPA receptor, neurocomputation.

Abbreviations: AMPA — H-amino-3-hydroxy-5-methyl-4-isoxazole propionate, AMPAR — AMPA receptor, AP — action potential, BCM - Bienenstock, Cooper, and Munro, BDNF — brain-derived neurotrophic factor, $(Ca^{2+})_i$ — intracellular concentration of Ca^{2+}, CaMKII — calcium/calmodulin-dependent kinase II, CREB - cAMP response element binding protein, EPSP — excitatory PSP, GR — glucocorticoid receptor, HFS — high-frequency stimulation, LFS — low-frequency stimulation, LTD — long-term depression, LTP — long-term potentiation, MAPK — mitogen-activated kinase, mGluR - metabotropic glutamate receptor, NMDA — N-methyl-D-aspartate, NMDAR — NMDA receptor, VSCC — voltage-sensitive Ca^{2+} channel, PKA — protein kinase A, PKC — protein kinase C, PSP — postsynaptic potential, PP1 — protein phosphatase 1, STDP — spike timing-dependent plasticity

Hebb's rule, neural networks and learning

To unravel the molecular and cellular bases of synaptic plasticity, which is putative learning and memory (L&M) mechanism, is an ambitious goal of neurobiology.

Donald Hebb (1949) predicted a form of synaptic plasticity driven by correlation of pre- and postsynaptic activity. He postulated that repeated activation of one neuron by another, across a particular synapse, increases its strength.

Neurobiology keeps inspiring computer science and vice versa. McCulloch and Pitts (1943) showed how a collection of simple, interconnected artificial neuron-like units could process information. In their first neural network all synaptic inputs converge onto a binary logical neuron. They proved that a sufficiently large number of these primitive logical devices, wired together in an appropriate way, are able of universal computation. Thus, it seems that the biological neural network must have a much greater computational capability. Rosenblatt (1958) showed that McCulloch-Pitts's network with modifiable synaptic weights can be learned for identifying and classifying objects. This network was capable of learning and he named it perceptron. Synaptic weights of perceptron are modified according to rule, which is similar to Hebb's learning rule.

Synaptic plasticity

Hebb's theoretical considerations and neurocomputational models proposed the idea that memories could be encoded in neural networks by changes in synaptic strength. At present, there are robust connectionist models that support this idea (Elgersma and Silva, 1999; Benuskova et al, 2001).

Exploring neurobiological data corresponding to this hypothesis started when Bliss and Lomo (1973) discovered long-term potentiation (long-lasting form of synaptic plasticity) in hippocampus.

Institute of Pathophysiology, Medical Faculty, Comenius University, Bratislava, Slovakia

Address for correspondence: Peter Jedlicka, MD, Institute of Pathophysiology LFUK, Sasinkova 4, SK-811 08 Bratislava, Slovakia.
Phone: +421.2.59357288

At present, it is widely accepted that origins and targets of connecting synapses are determined genetically as well as most of the properties of neurotransmission. However, the efficacy of signal transfer at synapses can change throughout life as a consequence of learning (Kandel, 2000). At present, bidirectional changes in the strength of synaptic responses are thought to be fundamental to information storage within neuronal networks.

Synaptic plasticity is a process in which synapses change their efficacy as a consequence of their previous activity. *Synaptic efficacy* (synaptic weight, synaptic strength) can be defined as an amplitude of the transmembrane voltage on the membrane of the postsynaptic neuron's soma which arises as a consequence of defined unit stimulation of the presynaptic terminal of the synapse (Benuskova, 1988). Synaptic efficacy is a measure of the synapse's contribution to the summary somatic postsynaptic potential which determines the time and frequency of the spike train generated after exceeding the excitation threshold of the neuron. Thus, it is directly proportional to the amplitude and duration of the postsynaptic potential (PSP) at the synapse. Synaptic weight (excitatory PSP after unit stimulation of the synapse) depends on two groups of factors (Benuskova, 1988; Kral, 1997):

A. Presynaptic factors: released amount of the transmitter
B. Postsynaptic factors: number of the receptors
types and properties of the receptors
input electric impedance (depends on the morphology of the dendritic spine and its electric properties)

Change of these synaptic properties leads to the change of synaptic strength. This change can be short or long-lasting and negative or positive.

Long-term plasticity

In many regions of the brain, long-term synaptic potentiation (LTP), a long-lasting increase in synaptic efficacy, is produced by high-frequency stimulation (HFS) of presynaptic afferents (Bliss and Lomo, 1973) or by pairing presynaptic stimulation with postsynaptic depolarization (Markram et al, 1997). Long-term synaptic depression (LTD), a long-lasting decrease in the strength of synaptic transmission, is produced by low-frequency stimulation (LFS) of presynaptic afferents. The majority of synapses in many brain regions and in many species that express LTP also express LTD. Thus, the regulation of synaptic strength by activity is bidirectional (Bear, 1996; Castellani et al, 2001).

Glutamate neurotransmitters released during afferent activity bind to AMPA, NMDA and metabotropic glutamate (mGlu) receptors to produce postsynaptic response. The intracellular Ca^{2+} level varies as Ca^{2+} enters the neuron via the VSCCs and NMDA receptor-channel complex, and as Ca^{2+} is released from internal storage sites as a result of the mGlu receptor-mediated G-protein cascade (Abraham and Tate, 1997; Zucker, 1999; Kim and Yoon, 1998). When the postsynaptic membrane is depolarized by the actions of the non-NMDA (AMPA) receptor channel (as occurs during high-frequency stimulation), the depolarization relieves the Mg^{2+} blockage of the NMDA channel. High-frequency afferent activity results in high levels of intracellular Ca^{2+}, which preferentially activate protein kinases (CaMKII, PKC, tyrosine kinase fyn); low-frequency afferent activity results in low levels of Ca^{2+}, which preferentially activate protein phosphatases (calcineurin, PP1). The induction of LTP and LTD appears to depend on the relative activity of kinases and phosphatases (Elgersma and Silva, 1999; Kim and Yoon, 1998). With both enzymes present, predominant kinase activity leads to LTP (via phosphorylation of various substrates) while predominant phosphatase activity leads to LTD. The intracellular calcium concentration [Ca2+]i is the principal trigger for the **induction** of LTD/LTP (Artola and Singer, 1993; Zucker, 1999).

NMDAR's coincidence detection and STDP

Calcium influx through NMDAR plays a crucial role in the induction of LTD/LTP. NMDAR is unique because its activation requires the presynaptic release of glutamate followed by postsynaptic depolarization (NMDAR is both receptor- and voltage-gated channel). It serves as a molecular coincidence detector for detecting the two simultaneous presynaptic a postsynaptic events, thus implementing Hebb's rule at the synapses (Tsien, 2000; Paulsen and Sejnowski, 2000). Conventional view for induction of LTP is that ‚strong' synaptic input (many synchronously active afferent fibers) produces a local depolarization that unblocks NMDARs. Concurrently released glutamate in neighboring synapses can activate the NMDAR providing the necessary Ca^{2+} signal Alternative model is based on backpropagating action potentials (Stuart and Sakman, 1994). Backpropagated APs (triggered by large EPSPs or by other inputs) could also provide postsynaptic depolarization for voltage-dependent relief of Mg^{2+} block of NMDARs (Magee and Johnston, 1997; Linden, 1999; Koester and Sakman, 1998). Experimental evidence indicates that long-term modification of synaptic efficacy can depend on the timing of pre- and postsynaptic APs (spike timing-dependent plasticity — STDP) (Song and Abbott, 2001). It has been shown that the temporal order of the synaptic input and the postsynaptic spike determines wether LTP or LTD is elicited. Repeated pairing of postsynaptic spiking after presynaptic activation results in larger Ca^{2+} influx and LTP (EPSP precedes the back-propagating AP), whereas postsynaptic spiking before presynaptic activation (EPSP follows the AP) leads to small Ca^{2+} transient and LTD (Markram et al, 1997; Bell et al, 1997; Bi and Poo, 1998; Debanne et al, 1998; Zhang et al, 1998; Egger et al, 1999; Zucker, 1999; Feldman, 2000). This temporally assymetric Hebbian synaptic plasticity supports sequence learning because it tends to wire together neurons that form causal chains (Paulsen and Sejnowski, 2000). Thus, NMDAR-gated modification of synaptic efficacy is essential for creating and stabilizing activity patterns in neural networks. Learned information or memory trace could be registered by the firing patterns of a group of neurons, which are most effectively connected (Tsien, 2000)..

The expression of LTD/LTP

The induction of associative LTP/LTD depends on Ca-dependent phosphorylation and dephosphorylation of various proteins. The mechanism for the *expression (maintenance)* of synaptic strength change has been hypothesized to depend on changes in the number and/or composition of the AMPARs in the postsynaptic membrane (Kandel, 2000). It involves an increase in the sensitivity and number of the postsynaptic non-NMDA (AMPA) receptors to glutamate as a result of being phosphorylated by the CaMKII. The expression (maintenance) of LTP and LTD may be mediated by reversible modulation of AMPA receptor GluR1 subunit phosphorylation. LTP and LTD are associated with phosphorylation and dephosphorylation, respectively, of distinct GluR1 phosphorylation sites (Lee et al, 2000). Phosphorylation of serine-831, the major CaMKII/PKC site, increases the single channel conductance of GluR1 AMPARs (Derkach et al, 1999). Another mechanisms are supported by recent studies that have shown that AMPARs are inserted or removed from the postsynaptic membrane after induction of LTP and LTD, respectively (Tao and Poo, 2001) and that receptor redistribution can also account for synaptic modification.

Since induction of LTP requires events only in the postsynaptic cell (Ca^{2+} influx through NMDA channels), whereas expression of LTP is due in part to a subsequent event in the presynaptic cells (increase in transmitter release), the presynaptic cells must somehow receive information that LTP has been induced. There is now evidence that Ca-activated second messengers, or perhaps Ca^{2+} itself, causes the postsynaptic cell to release one or more retrogade messengers (e.g. NO, BDNF) from its active dendritic spine (Kandel, 2000; Tao and Poo, 2001). They may modulate presynaptic release machinery, and the growth of new synapses.

LTP has phases. One stimulus train of action potentials leads to early, short-term phase of LTP (lasting 1—3 hours) by activating NMDARs, Ca^{2+} influx into postsynaptic cell, and a set of second messenger. This early component does not require protein synthesis. Four or more trains induce a more persistent phase of LTP (late LTP) that lasts for at least 24 hours. Late LTP requires new protein and RNA synthesis and recruits the cAMP-PKA-MAPK-CREB signaling pathway (Abel and Kandel, 1998; Kandel, 2000; Mayford and Kandel, 1999). With repeated trains the Ca2+ influx recruits an adenylyl cyclase, which activates the PKA leading to its translocation to the nucleus, where it phosphorylates the CREB protein. CREB in turn activates targets that are thought to lead to structural changes (the growth of new synaptic connections).

BCM neuron

Experimental data from the developing visual cortex have led to the formulation of a synaptic modification rule (Fig. 1), known as Bienestock-Cooper-Munro (BCM) rule (Bienenstock et al, 1982). The model has two main features:

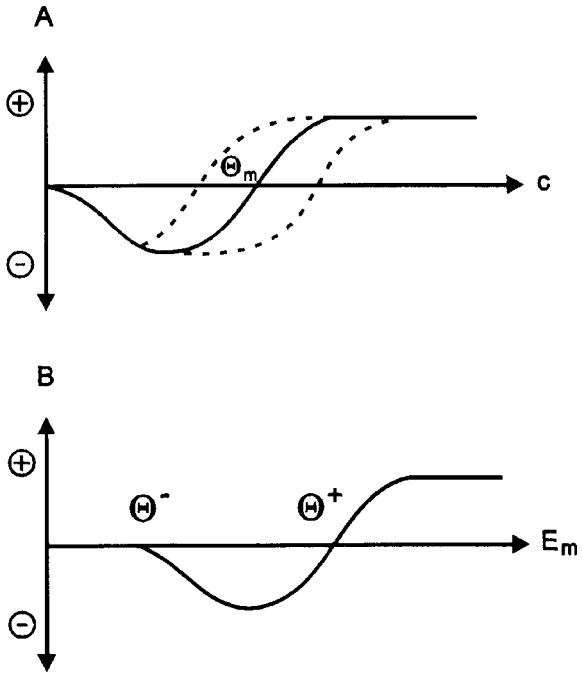

Fig. 1. A summary of synaptic modification rules.

First, it postulates that a *neuron possesses a synaptic modification threshold* (LTP/LTD threshold or θm), which dictates whether the neuron's acticity at any given instant will lead to strengthening or weakening of its input synapses. Thus, the modification threshold, θm determines the direction of synaptic efficacy change. Synaptic modification varies as a nonlinear (parabolic) function (Φ) of postsynaptic activity (c) which is defined as the product between presynaptic activity (x) and synaptic efficacy (w). Although the firing rate of a neuron c(t) depends in a nonlinear fashion on the postsynaptic potentials, BCM theory considers that the region between the excitation threshold and saturation may be reasonably approximated by a linear input-output relationship of the model neuron (Benuskova, 2001). The function Φ (c) changes sign at a particular value of c, that is the modification threshold θm. θm is the point of crossover from LTD to LTP. If postsynaptic activity is below θm (c<θm), but above baseline, Φ (c) is negative and synaptic efficacies are weakened. Conversely, if c exceeds θm, active synapses Φ (c) becomes positive and active synapses potentiate. For any value of c<θm, synaptic strength decays until it reaches 0.

$$\Phi (c(t), \theta m(t)) = c(t) [c(t) - \theta m(t)]; \qquad c(t) = \Sigma\, x(t)w(t);$$

$$\Delta w = \eta \Phi x \text{ (}\eta\text{ is the modification rate)}$$

Synaptic weight (w) changes according to Hebb's learning rule which requires correlate pre- and postsynaptic activity at the synapse.

ABS neuron

A moderate rise in $(Ca^{2+})_i$ should lead to a predominant activation of phosphatases (and LTD) while a stronger increase would favour activation of kinases (and LTP, Lisman 1989). Experimental data suggest that there are two voltage dependent thresholds for LTD and LTP corresponding to changes in $(Ca^{2+})_i$. If the first voltage-dependent 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.

Artola, Brocher and Singer formulated a synaptic plasticity model (related to BCM theory) which defines two thresholds (θ- and θ+) according to these experimental data. Their synaptic modification rule is referred to as the ABS rule (Artola and Singer, 1993): the direction of the synaptic gain change depends on the membrane potential of the postsynaptic cell, or on the amplitude of the surge of $(Ca^{2+})_i$. If the first threshold θ- is reached, a mechanism is activated that leads to LTD. If the second threshold θ+ is reached, another process is triggered that leads to LTP.

There is also another important difference between BCM and ABS rule. If $(Ca^{2+})_i$ is the only relevant variable for the induction of LTD/LTP it follows that it should not matter whether the depolarization required for Ca^{2+} influx (through NMDAR and VSCC) is caused by the acticity of the very synapses that are going to be modified or by that of other synaptic inputs. Thus, the ABS-LTD/LTP curve can be extended to heterosynaptic modifications. ABS rule permits synaptic changes to occur at inputs that are themselves inactive because θ- can be reached by depolarization spread (or Ca^{2+} spread) from adjacent active synapses. Therefore 'extended' ABS rule postulates that the direction of synaptic changes is also a function of the activation of other (heterosynaptic) inputs that are not going to be modified. The effect of increasing the activity of other inputs is a gradual shift to the left of the curve. As heterosynaptic activity increases less and less activation of the homosynaptic input is required to reach the thresholds for LTD (θ-) and LTP (θ+). And eventually threshold θ- will be reached at synapses even if they are not active themselves, that is, heterosynaptic depression occurs. Thus, ABS rule can account for both homosynaptic and heterosynaptic LTD and LTP.

Sliding modification threshold and metaplasticity

The second important feature of the BCM rule is that the value of θm is not fixed but instead increases according to a nonlinear function with the average output of the cell (Kim and Yoon, 1998; Benuskova, 2001; Artola and Singer, 1993). θm varies according to a (running) time average of prior postsynaptic activity, i.e. θm is a sliding modification threshold. The current value of θm changes proportionally to the square of the neuron's activity averaged over some recent past: $\theta m(t) = \alpha < c^2(t) > \tau$. θm slides as a function of the prior history of the postsynaptic cell. The sliding threshold is a homeostatic mechanism which keeps the modifiable synapses within a useful dynamic range (Abraham et al, 2001). It acts against Hebbian positive-feedback process in which effective synapses are strenghtenend, making them even more effective, and ineffective synapses are weakened, making them less so. This tends to destabilize postsynaptic firing rates, reducing them to zero or increasing them excessively. BCM stabilizes Hebbian plasticity by negative-feedback — the LTP threshold increases (elevates, slides rightward) if the postsynaptic neuron is highly active, making LTP more difficult and LTD easier to induce (Abbott, 2000; Abraham, 1997). The inverse process occurs when the activity of the postsynaptic neuron is reduced.

Thus, the modification threshold θm, which regulates the ability to undergo LTP/LTD is itself regulated. The term "**metaplasticity**" has been introduced recently to describe the changes in the ability to undergo LTP and LTD (Abraham, 1996). It has become apparent from experimental data that the synaptic plasticity can be altered by previous synaptic activity, or by neuromodulators. It is thus itself plastic, and therefore termed "metaplasticity". The induction of metaplasticity corresponds to sliding BCM modification threshold. Metaplasticity is the plasticity of synaptic plasticity (plasticity at a higher level). For example, previous stimuli may make it easier or harder to induce LTP. The induction of metaplasticity does not change synaptic efficacy but affects synaptic physiology in such a way that subsequent attempts to induce synaptic plasticity will be modified.

Do the synaptic plasticity and metaplasticity experimental data fit the BCM model?

The BCM theory makes several explicit assumptions about how synapses modify, and these have helped to guide experiments in a number of systems. In many regards, there does appear to be a good correspondence.

First, (θm exists) there is evidence in both hippocampus and visual cortex that the frequency of afferent activity is one variable that generates a bidirectional pattern of LTD and LTP induction very similar to that predicted by the BCM model (Dudek and Bear, 1992; Kirkwood et al, 1993).

Second, (θm slides) the threshold θm does indeed appear to be adjustable, depending on the prior history of synaptic activity. Numerous studies have shown that prior activation of glutamate receptors modifies the level of LTD/LTP threshold (Fujii et al, 1991; Huang et al, 1992; Cohen and Abraham, 1996; Kirkwood et al, 1996; Abraham, 1997).

Third, BCM modification threshold has two important characteristics: (a) *the change of modification threshold occurs* for all excitatory synapses terminating on the affected neurons, i.e., it occurs *heterosynaptically,* regardless of which inputs are overactive or quiescent (b) the direction and degree of threshold metaplastic change *is a function of time-averaged postsynaptic cell firing.* (a) Recent experiments have demonstrated that LTP threshold can be modified heterosynaptically in vitro (Holland and Wagner, 1999; Wang and Wagner, 1999) and in vivo (Abraham et al, 2001). (b) Abraham et al (2001) also showed that cell firing is critical to sliding the LTP threshold.

In addition, powerful BCM neurocomputational models of synaptic plasticity, consistent with experimental findings, were developed (Benuskova et al, 1994, 2001). Thus, many experimental results suggest that the BCM theory may be a general synaptic plasticity rule which could be relevant to synaptic models of learning in the visual cortex, hippocampus and also in other (mature) brain regions (Benuskova et al, 1994; Kim and Yoon, 1998; Castellani et al, 2001). However, further experiments and theoretical considerations are needed to refine the BCM model.

What could be the molecular mechanism for metaplasticity?

There are many candidate mechanisms underlying metaplasticity, because any molecular action, which affects characteristics of $(Ca^{2+})_i$ change, might influence both plasticity and metaplasticity (Abraham and Tate, 1997). We will mention only three main candidates:

1. NMDAR is the critical point of postsynaptic calcium entry, which plays a fundamental role in the synaptic modification. As such, *changes in NMDAR function* will dramatically alter the properties of activity-dependent synaptic plasticity and could explain metaplasticity. The composition (subunit ratio of NR2A/NR2B) and function of synaptic NMDARs can be acutely and bidirectionally modified by cortical activity (Carmignoto and Vicini, 1992; Quinlan et al, 1999 a, b; Philpot et al, 2001). Manipulations which do potentiate NMDAR function, such as mGluR activation, facilitate shifting the LTP threshold to the left (Cohen and Abraham, 1996). It is interesting that separate NMDAR and mGluR activation produces different forms of metaplasticity, LTP inhibition in the case of NMDAR activation and LTP facilitation by mGluR activation.

2. *Change in Ca^{2+} buffering capacity* of the cell is another canditate underlying metaplasticity (Chard et al, 1995; Gold and Bear, 1994). Up-regulation of Ca-binding proteins (calbindin and calcineurin) as a mechanism for sliding the threshold θm was not supported by recent experiments (Abraham et al, 2001). These data, however, do not rule out a translocation of existing calcium-binding proteins to sites where they can more effectively buffer the calcium critical for LTP generation.

3. Data from CaMKII transgenic mice suggest that Ca^{2+} influx and *CaMKII* might be involved in affecting θm (Mayford et al, 1995). Increased intracellular Ca^{2+} results in autophosphorylation of CaMKII, thereby converting the enzyme to a Ca^{2+} independent (autonomous) form (Abraham and Tate, 1997). It has been proposed, that the level of Ca^{2+} independent CaMKII sets the value of θm (Bear, 1995; Mayford et al, 1995; Glazewski et al, 2001). It appears that higher level of autonomous CaMKII shifts the LTP threshold to the right and so the subsequent incoming signal may be less effective in inducing LTP. Phosphorylated CaMKII binds Ca^{2+} and calmodulin more tightly and limits the availability of Ca^{2+} and calmodulin for other enzymes essential for LTP to be established. This may result in a metaplastic state such that a second burst of synaptic activity might lead to a lower net elevation in Ca^{2+} concentration that could be now in the range for selective activation of specific phosphatases. This would reduce signaling events dependent upon the kinase, such as the phosphorylation of the AMPAR. In this way the induction of LTD may be facilitated (Abraham and Tate, 1997).

It appears that the threshold θm may be modified not only by prior history of synaptic activity but also by various **modulatory factors** like various neurotrasmitters, circulating hormones, etc. E.g. binding of corticosteroids to its glucocorticoid receptor results in a shift of the LTP modification threshold to the right, and a shift of the LTD modification threshold to the left (Kim et al, 1996). Stress and glucocorticoids appear to exert a metaplastic effect through the modulation of Ca^{2+} levels. These data indicate that θ-, postulated by Artola, Broecher, Singer (Artola and Singer, 1993), may be modifiable as well as θm (θ+) and that a single stimulus such as GR activation may shift these two thresholds in opposite directions.

Castellani et al (2001) presented recently an interesting *biophysical model* that combines and integrates bidirectional plasticity of AMPAR by calcium-dependent phosphorylation and dephosphorylation, (LTP/LTD induction) with plasticity of NMDAR subunit composition. The fundamental assumption of the model is that the intracellular calcium concentration is the principal trigger for the induction of LTD/LTP, an assumption that has wide experimental support. According to the model the AMPAR conductance depends on the level of intracellular Ca^{2+}, which regulates the activity of protein kinases and protein phosphatases that target the two sites on the GluR1 protein. Castellani et al demonstrate that the modification of NMDAR subunit composition may account for metaplasticity.

Their model produces a frequency-dependent LTP/LTD curve with a sliding synaptic modification threshold similar to the BCM theory. Further experiments are needed to test the assertions and predictions of the model.

Questions to be answered

Despite of many new findings there are still various questions to be answered and further experiments to be done. The *mechanisms of synaptic plasticity* are still not completely clear — the role of retrograde messengers, details in the molecular cascades leading to gene expression and new protein synthesis or to growth of new synapses, finding the more accurate causal connection between plasticity and various forms of learning and memory, etc. The use of regulated and anatomically restricted genetic modification, combined with phenotypic analysis, should provide a powerful set of tools for elucidating synaptic plasticity mechanisms (Mayford and Kandel, 1999). *Mechanisms of metaplasticity* are even more unclear and they remain to be fully characterized. There are many interesting *stimuli* also *for neurocomputation.* For example it would be worth to understand consequences of the BCM algorithm in computational models of hippocampus-dependent memory formation (Abraham et al, 2001) or to study computational consequences of the temporally asymmetric Hebbian learning rule and its ability to create and stabilize activity patterns in neural assemblies.

Mechanisms underlying long-term changes in synaptic function are likely to be at the heart of many cognitive and emotional processes in humans (Kandel, 2000). Therefore, molecular and cellular insights into learning and memory undoubtedly will have a profound impact on the *understanding and treatment of psychiatric disorders.*

The BCM theory made several assumptions about how synapses modify and these have helped to guide various neurobiological and neurocomputational experiments. Conversely, the results of these experiments suggested ways how to refine the theoretical BCM. Thus, the BCM model of synaptic plasticity is an excellent example of the *fruitfulness of the tight interaction* between **theoretical** considerations, *neurobiological* experiments and *neurocomputational* models.

References

Abbott LF, Nelson SB. Synaptic plasticity: taming the beast. Nat Neurosci 2000; 3 (Suppl): 1178—1183.

Abel T, Kandel E. Positive and negative regulatory mechanisms that mediate long-term memory storage. Brain Res Brain Res Rev 1998; 26 (2—3): 360—378.

Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci 1996; 19 (4): 126—130.

Abraham WC, Mason-Parker SE, Bear MF, Webb S, Tate WP. Heterosynaptic metaplasticity in the hippocampus in vivo: a BCM-like modifiable threshold for LTP. Proc Natl Acad Sci USA 2001; 98 (19): 10924—1099.

Abraham WC, Tate WP. Metaplasticity: a new vista across the field of synaptic plasticity. Prog Neurobiol 1997; 52 (4): 303—323.

Artola A, Singer W. Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation. Trends Neurosci 1993; 16 (11): 480—487.

Bear MF. Mechanism for a sliding synaptic modification threshold. Neuron 1995; 15 (1): 1—4.

Bear MF, Cooper LN, Ebner FF. A physiological basis for a theory of synapse modification. Science 1987; 237 (4810): 42—48.

Bell CC, Han VZ, Sugawara Y, Grant K. Synaptic plasticity in a cerebellum-like structure depends on temporal order. Nature 1997; 387 (6630): 278—281.

Benuskova L. Mechanisms of synaptic plasticity. Ces Fysiol 1988; 37 (5): 387—400.

Benuskova L, Diamond ME, Ebner FF. Dynamic synaptic modification threshold: computational model of experience-dependent plasticity in adult rat barrel cortex. Proc Natl Acad Sci USA 1994; 91 (11): 4791—4795.

Benuskova L, Rema V, Armstrong-James M, Ebner FF. Theory for normal and impaired experience-dependent plasticity in neocortex of adult rats. Proc Natl Acad Sci USA 2001; 98 (5): 2797—2802.

Bi GQ, Poo MM. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. J Neurosci 1998; 18 (24): 10464—1072.

Bienenstock EL, Cooper LN, Munro PW. Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. J Neurosci 1982; 2 (1): 32—48.

Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 1973; 232 (2): 331—356.

Carmignoto G, Vicini S. Activity-dependent decrease in NMDA receptor responses during development of the visual cortex. Science 1992; 258 (5084): 1007—1011.

Castellani GC, Quinlan EM, Cooper LN, Shouval HZ. A biophysical model of bidirectional synaptic plasticity: dependence on AMPA and NMDA receptors. Proc Natl Acad Sci USA 2001; 98 (22): 12772—12777.

Chard PS, Jordan J, Marcuccilli CJ, Miller RJ, Leiden JM, Roos RP, Ghadge GD. Regulation of excitatory transmission at hippocampal synapses by calbindin D28k. Proc Natl Acad Sci USA 1995; 92 (11): 5144—5148.

Cohen AS, Abraham WC. Facilitation of long-term potentiation by prior activation of metabotropic glutamate receptors. J Neurophysiol 1996; 76 (2): 953—962.

Debanne D, Gahwiler BH, Thompson SM. Long-term synaptic plasticity between pairs of individual CA3 pyramidal cells in rat hippocampal slice cultures. J Physiol 1998; 507 (1): 237—247.

Derkach V, Barria A, Soderling TR. Ca^{2+}/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. Proc Natl Acad Sci USA 1999; 96 (6): 3269—3274.

Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA 1992; 89 (10): 4363—4367.

Egger V, Feldmeyer D, Sakmann B. Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex. Nat Neurosci 1999; 2 (12): 1098—1105.

Elgersma Y, Silva AJ. Molecular mechanisms of synaptic plasticity and memory. Curr Opin Neurobiol 1999; 9 (2): 209—213.

Feldman DE. Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. Neuron 2000; 27 (1): 45—56.

Fujii S, Saito K, Miyakawa H, Ito K, Kato H. Reversal of long-term potentiation (depotentiation) induced by tetanus stimulation of the input to CA1 neurons of guinea pig hippocampal slices. Brain Res 1991; 555 (1): 112—122.

Glazewski S, Bejar R, Mayford M, Fox K. The effect of autonomous alpha-CaMKII expression on sensory responses and experience-dependent plasticity in mouse barrel cortex. Neuropharmacology 2001; 41 (6): 771—778.

Gold JI, Bear MF. A model of dendritic spine Ca^{2+} concentration exploring possible bases for a sliding synaptic modification threshold. Proc Natl Acad Sci USA 1994; 91 (9): 3941—3945.

Hebb D. The Organization of Behavior. J. Wiley and Sons, New York, 1949.

Holland LL, Wagner JJ. Primed facilitation of homosynaptic long-term depression and depotentiation in rat hippocampus. J Neurosci 1998; 18 (3): 887—894.

Huang YY, Colino A, Selig DK, Malenka RC. The influence of prior synaptic activity on the induction of long-term potentiation. Science 1992; 255 (5045): 730—733.

Johnston D, Hoffman DA, Colbert CM, Magee JC. Regulation of back-propagating APs in hippocampal neurons. Curr Opin Neurobiol 1999; 9: 288—292.

Kandel ER. Cellular mechanisms of learning and the biological basis of individuality. In: Principles of Neural Science, pp. 1247—1279. Eds. Kandel ER, Schwartz JH, Jessel TM. McGraw—Hill 2000.

Kim JJ, Foy MR, Thompson RF. Behavioral stress modifies hippocampal plasticity through N-methyl-D-aspartate receptor activation. Proc Natl Acad Sci USA 1996; 93 (10): 4750—4753.

Kim JJ, Yoon KS. Stress: metaplastic effects in the hippocampus. Trends Neurosci; 21 (12): 505—509.

Kirkwood A, Dudek SM, Gold JT, Aizenman CD, Bear MF. Common forms of synaptic plasticity in the hippocampus and neocortex in vitro. Science 1993; 260 (5113): 1518—1521.

Kirkwood A, Rioult MC, Bear MF. Experience-dependent modification of synaptic plasticity in visual cortex. Nature 1996; 381 (6582): 526—528.

Koester HJ, Sakmann B. Calcium dynamics in single spines during coincident pre- and postsynaptic activity depend on relative timing of back-propagating action potentials and subthreshold excitatory postsynaptic potentials. Proc Natl Acad Sci USA 1998; 95 (16): 9596—9601.

Kral A. Neurónové siete a nervový systém. In: Úvod do teórie neurónových sietí, pp. 11—31. Eds. Kvasnička V, Beňušková Ľ, Farkaš I, Pospíchal J, Tiňo P, Kráľ A. IRIS, Bratislava 1997.

Lee HK, Barbarosie M, Kameyama K, Bear MF, Huganir RL. Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. Nature 2000; 405 (6789): 955—959.

Linden DJ. The return of the spike: postsynaptic APs and the induction of LTP and LTD. Neuron 1999; 22 (4): 661—666.

Magee JC, Johnston D. A synaptically controlled associative signal for Hebbian plasticity in hippocampal neurons. Science 1997; 275: 209—213.

Markram H, Lubke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 1997; 275: 213—215.

Mayford M, Kandel ER. Genetic approaches to memory storage. Trends Genet 1999;15 (11): 463—470.

Mayford M, Wang J, Kandel ER, O'Dell TJ. CaMKII regulates the frequency-response function of hippocampal synapses for the production of both LTD and LTP. Cell 1995; 81 (6): 891—904.

McCulloch WS, Pitts W. A logical calculus of the ideas immanent in nervous activity. Bull Mathemat Biophys 1943; 5: 115—133.

Paulsen O, Sejnowski TJ. Natural patterns of activity and long-term synaptic plasticity. Curr Opin Neurobiol 2000; 10 (2): 172—179.

Philpot BD, Sekhar AK, Shouval HZ, Bear MF. Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. Neuron 2001; 29 (1): 157—169.

Quinlan EM, Philpot BD, Huganir RL, Bear MF. Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex in vivo. Nat Neurosci 1999; 2 (4): 352—357.

Quinlan EM, Olstein DH, Bear MF. Bidirectional, experience-dependent regulation of N-methyl-D-aspartate receptor subunit composition in the rat visual cortex during postnatal development. Proc Natl Acad Sci USA 1999; 96 (22): 12876—12880.

Rosenblatt F. The Perceptron, a probabilistic model for information storage and organization in the brain. Psychol Rev 1948; 62: 386—408.

Song S, Abbott LF. Cortical development and remapping through spike timing-dependent plasticity. Neuron 2001; 32 (2): 339—350.

Stuart GJ, Sakmann B. Active propagation of somatic action potentials into neocortical pyramidal cell dendrites. Nature 1994; 367 (6458): 69—72.

Tao HW, Poo M. Retrograde signaling at central synapses. Proc Natl Acad Sci USA 2001; 98 (20): 11009—11015.

Tsien JZ. Linking Hebb's coincidence-detection to memory formation. Curr Opin Neurobiol 2000; 10 (2): 266—273.

Zhang LI, Tao HW, Holt CE, Harris WA, Poo M. A critical window for cooperation and competition among developing retinotectal synapses. Nature 1998; 395 (6697): 37—44.

Zucker RS. Calcium- and activity-dependent synaptic plasticity. Curr Opin Neurobiol 1999; 9 (3): 305—313.

Received October 8, 2001.
Accepted March 3, 2002.