Synaptic Plasticity in the Amygdala

Comparisons with Hippocampus

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ABSTRACT: Long-term potentiation (LTP) is a widely studied form of synaptic plasticity, and a considerable amount of evidence indicates that it could be involved in learning and memory. Intensive investigation of this phenomenon in the hippocampus has yielded tremendous insight into the workings of synapses in the mammalian central nervous system, but important questions remain to be answered. The most important of these are: (1) whether LTP is the basis of learning and memory, and (2) how similar are the induction, maintenance, and expression mechanisms in the rest of the brain to those in the hippocampus. Because the most important strategy for linking LTP to learning involves disrupting the mechanisms of LTP and examining the consequences on behavior, it is likely that the first question cannot be answered until the second has been addressed. Recent evidence indicates that although the general processes have much in common, significant differences exist among forebrain structures, including the hippocampus, basolateral amygdala, and ventral striatum. It is clear that the roles of receptors and calcium channels, kinases, and transcription factors vary within these structures, reflecting the different functions of these brain regions.

KEYWORDS: long-term potentiation; NMDA receptors; calcium-calmodulin-dependent protein kinase; RasGRF-1; MAP kinase; learning and memory

INTRODUCTION: THE FUNCTIONAL SIGNIFICANCE OF LONG-TERM POTENTIATION

Long-term potentiation (LTP) is, almost by default, the best model for learning related plasticity in the mammalian central nervous system. A significant body of evidence supports the hypothesis that activity-dependent synaptic plasticity is responsible for, plays a role in, or at least shares important features with learning and memory.[1] On the other hand, there has been no single convincing demonstration that LTP *is* the mechanism of learning and memory, and there may never be.

One difficulty in establishing a simple link between LTP and learning is that there may be as many different mechanisms and expressions of use-dependent plasticity

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Ann. N.Y. Acad. Sci. 985: 114–124 (2003).

as their are different forms of learning. By determining which features of use-dependent plasticity are common to forebrain synapses and which are more restricted to one type of synapse or another, we can make better use of the tools available to us and come to a broader understanding of the nature of both neuronal plasticity and behavior. As an early step in this process, we have explored the different roles of neurotransmitter receptors and cytoplasmic signaling molecules in the induction and maintenance of LTP in the amygdala and the hippocampus. Our results indicate significant differences between the two structures that should be taken into account when considering the behavioral consequences of genetic or pharmacological manipulations that affect synaptic plasticity.

Although the methods used to test the links between LTP and learning have evolved over time, the basic approaches remain the same. By observing synaptic plasticity and learning and determining whether they covary with behavioral manipulations, we can establish whether the same manipulations have the same effects.[2] By inducing LTP artificially, it is possible to determine whether the mechanisms of synaptic plasticity interact with those of learning by either facilitating or inhibiting behavioral change.[3] Finally, and most commonly, the lesion approach is well suited to these investigations. In the same way that ablation of specific brain regions can contribute to our understanding of the function of those regions, we can establish some of the parameters of the relation between LTP and learning by preventing the induction or maintenance of LTP through pharmacologic[4,5] or genetic[6–8] manipulations and by examining the consequences for learning and memory.

Within this general framework, it is important that we understand as much as possible about both LTP and learning. To define learning and memory as a single phenomenon ignores the fact that despite their common features, enormous differences exist between, for example, declarative and nondeclarative memory.[9] Similarly, defining LTP simply in terms of the response of CA1 synapses to high-frequency stimulation almost certainly overlooks important phenomenological and mechanistic differences that will have great functional significance.

In this context, a broad survey of the phenomena and mechanisms of LTP could be justified. More useful, however, is to choose a small set of brain structures that can be related more directly to well-characterized forms of learning and memory, that represent significantly different cytoarchitectural and neurochemical profiles, and that are amenable to investigation *in vivo* and *in vitro*. The most suitable structure to examine after the hippocampus, therefore, should be the amygdala.

LONG-TERM POTENTIATION IN THE AMYGDALA AND HIPPOCAMPUS

Years of research into the mechanisms of LTP in the hippocampus have created some degree of consensus, at least about what types of molecules and cellular processes are involved.[10] Because LTP is induced by synaptic activity, it is clear that some cytoplasmic membrane-bound molecule(s) will be required to transduce extracellular signals into activation of intracellular processes. This process is almost certainly dependent on (or strongly regulated by) intracellular calcium,[11] so calcium and calcium-dependent processes should be recruited. Eventually, long-term expression of LTP requires protein synthesis,[12] and therefore some molecules will be re-

quired to link more transient signals to the activation of specific genes that may be involved in growth or restructuring of potentiated synapses.

Apart from these generalities, however, it is most likely that morphologically and physiologically distinct types of synapses will have evolved different sets of molecular pathways for initiating and maintaining synaptic plasticity. In fact, at each step in the pathway from extracellular signal to gene expression, there is evidence of differences between LTP in CA1 and in the basolateral amygdala.

Receptors and Channels

Hippocampus

One of the most commonly reported (and agreed upon) findings in the LTP field is that blocking NMDA receptors prevents LTP of Schaffer collateral synapses onto CA1 pyramidal neurons,[13,14] except under rather extraordinary conditions.[15] NMDA receptor antagonists such as AP5 or CPP prevent the induction of LTP in CA1 by a variety of stimuli, including tetanus (e.g., 100 Hz for 1 second), theta burst (clusters of 4–6 stimuli delivered at high frequency and repeated at 5 Hz), or pairing of direct depolarization of the postsynaptic cell with low-frequency stimulation. (For a review, see Ref. 16.)

Mice with targeted deletion of NMDA receptor subunits also demonstrated deficits in LTP in CA1.[17] Mice with deletion of the NR1 subunit (which is required for the receptor to function) using conventional gene targeting die before birth.[18] When NR1 knockout is restricted to the CA1 region,[19] it abolishes both NMDA-mediated synaptic currents and LTP induction.

Voltage-gated calcium channels (VGCCs) can also participate in the induction of LTP in CA1, although their contribution is typically only detectable when strong tetanic stimulation is used.[15] Interestingly, some of the calcium-dependent downstream signaling pathways that are implicated in LTP induction and maintenance can be selectively recruited by either NMDA-receptor–gated or VGCC-activated calcium influx. For example, mice with point mutations that affect the function of calcium-calmodulin–dependent protein kinase II (aCaMKII) show small residual LTP in CA1 that is not sensitive to NMDA antagonists.[20] On the other hand, Ca^{2+} entering through VGCCs appears to activate protein kinase C (PKC) selectively.[21]

Even within the hippocampus, induction mechanisms differ significantly from CA1 to CA3.[22] CA3 pyramidal neurons receive three types of excitatory synapses on their apical dendrites; recurrent collaterals from CA3 efferent axons, associational and commissural inputs, and mossy fiber inputs from dentate gyrus granule cells. Associational/commissural inputs appear to behave like Schaffer collateral inputs to CA1 in that LTP induction is blocked by NMDA-receptor antagonists,[23] but there is general agreement that the induction and/or expression mechanisms of mossy fiber LTP are different. Although glutamate released from mossy fibers binds to and activates NMDA receptors,[24] this does not appear to participate in the induction of mossy fiber LTP, as NMDA antagonists have no effect. Some controversy exists over whether the induction of mossy fiber LTP requires postsynaptic depolarization and calcium influx,[25] but there is general agreement that the expression of LTP at these synapses has a major presynaptic component.

Amygdala

In the amygdala, there is evidence both for and against an important role for NMDA receptors in the induction of LTP.[26] Clearly, it is important to define which nuclei and which synapses within those nuclei (where possible) are being activated, as there is likely to be at least as much diversity among synapses in the amygdala as in the hippocampus. Chapman and Bellavance[27] initially reported that the NMDA antagonist AP5 blocked LTP in the basolateral amygdala in response to stimulation of the external capsule (putatively cortical inputs) but only at concentrations that also affected synaptic responses evoked at low frequency. Concentrations that were known to block LTP in CA1 were without effect on either baseline synaptic transmission or LTP. Other laboratories have provided support for the contention that at least some significant percentage of LTP in the lateral and basolateral amygdala is NMDA independent.[28,29] Others have reported LTP in the lateral or basolateral amygdala that is completely blocked by NMDA antagonists.[30] Weisskopf and LeDoux[31] offered an interesting insight into the nature of this discrepancy by showing that NMDA receptors activated by cortical and thalamic inputs to lateral amygdala neurons produce distinctly different whole-cell responses, suggesting that they might make differential contributions to the induction of LTP.

Recently, we investigated LTP in BLA using field potential recordings and stimulation of inputs that are likely to include a mixture of thalamic and intrinsic (from LA) fibers.[32] The results, once again, present an intermediate position that is not consistent with a simple model of LTP induction in the amygdala. Bath application of 50 M D-AP5 produces a reduction in the amplitude and slope of baseline responses evoked at 0.033 Hz (FIG. 1). Theta-burst stimulation (TBS) delivered in the presence of AP5 produces LTP that is significantly greater than baseline, but also significantly smaller than TBS given in normal medium. To complicate matters further, 20-minute bath application of 50 M D-AP5 in the absence of TBS produces a significant increase in baseline responses. Superimposed on these increases, it is difficult to determine if the potentiation seen in the presence of AP5 is induced by tetanic stimulation.

The lack of a complete block of LTP induction by AP5 suggested that VGCCs may contribute significantly to LTP in BLA. Using intracellular recording and an induction protocol that involved pairing of direct depolarization with stimulation of the thalamic inputs to the lateral amygdala, Weisskopf *et al.*[29] produced potentiation that was associative and restricted to the synaptically activated inputs. The resulting LTP was not affected by either AP5 or the noncompetitive NMDA antagonist MK-801, but it was blocked by either the L-channel blocker nifedipine or by intracellular calcium chelation with BAPTA. When synaptic responses were recorded as extracellular field potentials and stimulation applied to the lateral amygdala, application of 30 M nimodipine was without effect on either baseline synaptic responses or LTP (FIG. 2A).[32] The combination of 50 M D-AP5 and 30 M nimodipine, however, completely blocked the induction of LTP (FIG. 2B). It appears, therefore, that both NMDA receptors and VGCCs contribute to LTP induction by standard tetanic or TBS. Whether this is because extracellular stimulation and recording always activate a heterogeneous group of inputs or because each input pathway uses both induction mechanisms remains to be tested.

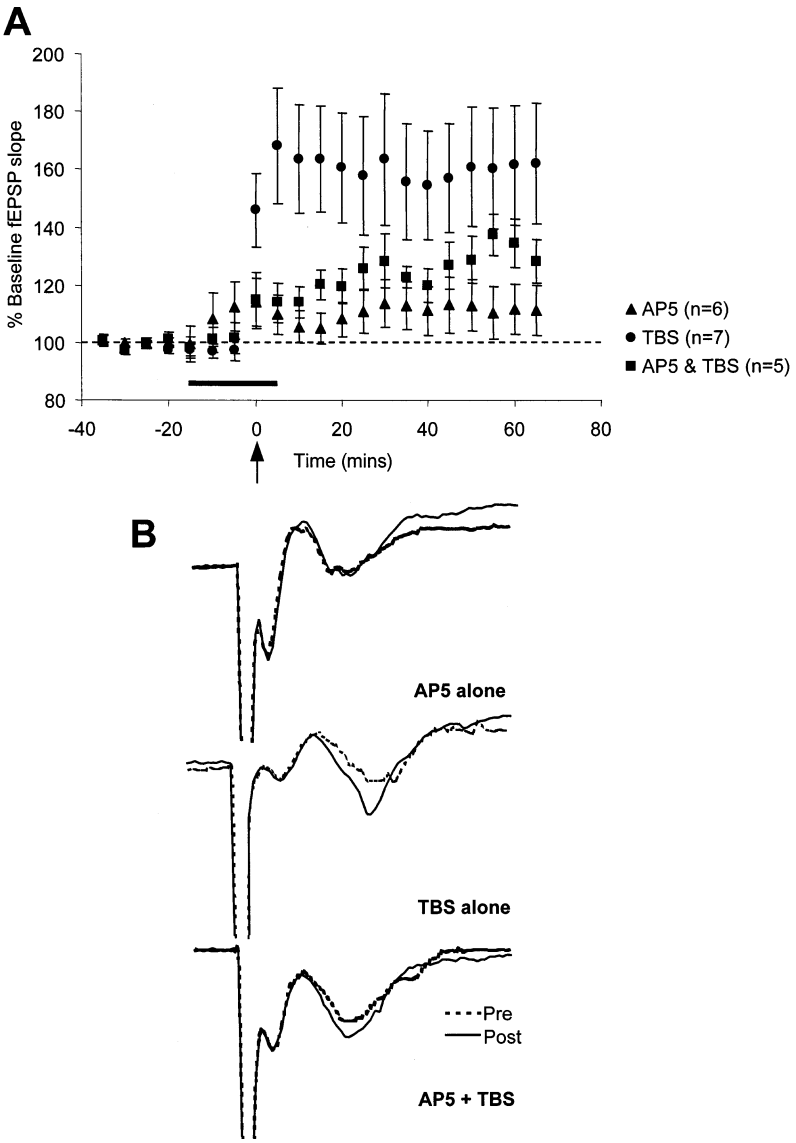

FIGURE 1. D-AP5 50 mM reduces the magnitude of LTP in basolateral amygdala. (**A**) AP5 refers to the group treated with 50 mM D-AP5 only, theta-burst stimulation (TBS) to the group that received TBS only, and AP5 and TBS to the group that received TBS in the presence of 50 mM D-AP5. The *horizontal dashed line* indicates the baseline level (100%). The *thick black horizontal line* indicates the period of AP5 infusion, where appropriate. The *arrow* (at time 0) indicates delivery of TBS, where appropriate. The n's refer to the number of animals tested. (**B**) Examples of extracellular field potential responses before and after drug administration and/or TBS.

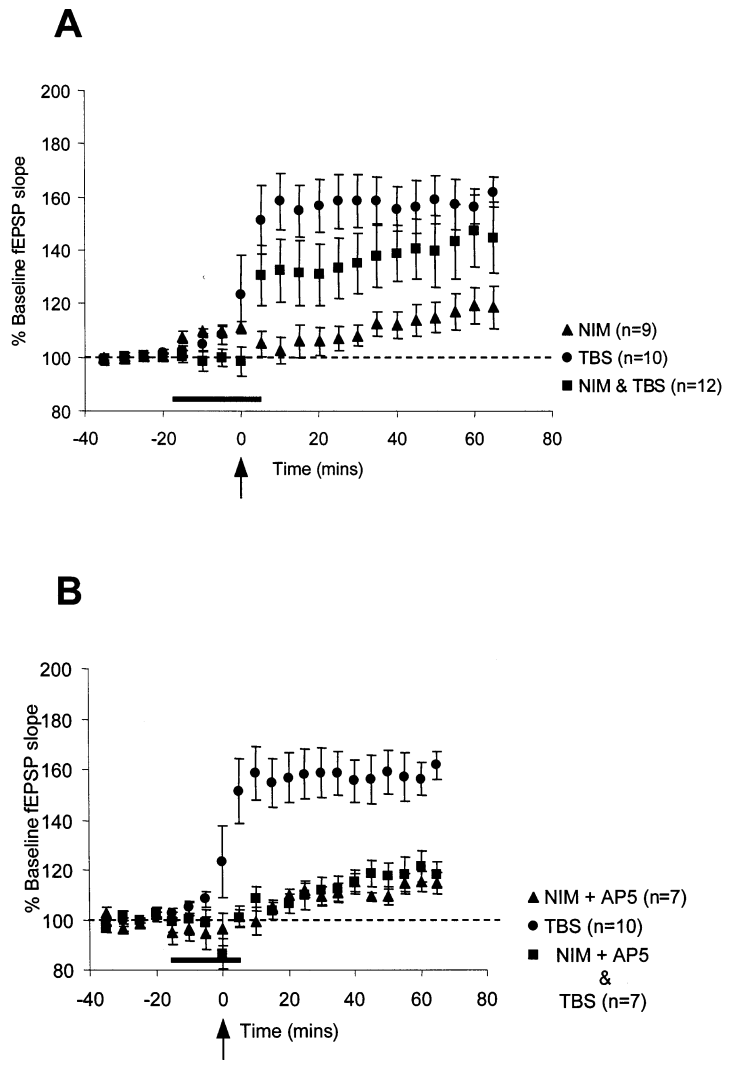

FIGURE 2. D-AP5 nimodipine 30 and 50 mM blocks LTP in the basolateral amygdala. In both figures, the *horizontal dashed line* indicates the baseline level (100%). The *thick black horizontal line* indicates the period of drug infusion, where appropriate. The *arrow* (at time 0) indicates delivery of TBS, where appropriate. The n's refer to the number of animals tested. (**A)** NIM refers to the group treated with 30 mM nimodipine only, TBS to the group that received TBS only, and nimodipine and TBS to the group that received TBS in the presence of 30 mM nimodipine. (**B)** Drug refers to the group treated with 30 mM nimodipine and 50 mM D-AP5 only, TBS to the group that received TBS only, and drug and TBS to the group that received TBS in the presence of 30 mM nimodipine and 50 mM D-AP5.

CaMKII

Because LTP in CA1 depends on increases in intracellular calcium, it is logical to assume that events that follow the initial induction of LTP should involve calcium-dependent molecules. One of the most logical candidates was the calcium/calmodulin–dependent protein kinase (CaMKII), an enzyme activated by changes in intracellular calcium that is abundant in the postsynaptic density.[33] CaMKII also has the ability to phosphorylate itself, thereby reducing its dependence on elevated calcium concentrations, a useful property for a molecule involved in converting a transient signal into a long-lasting change in synaptic function.[34] Injection of peptide inhibitors of CaMKII into CA1 pyramidal neurons blocks the induction of LTP,[35] as does complete deletion of the aCaMKII gene (expressed postnatally and primarily in the forebrain).[8] A single amino acid substitution (alanine for threonine^{286}) renders aCaMKII unable to autophosphorylate and almost completely abolishes CA1 LTP,[20] suggesting that autophosphorylation is necessary for even the early stages of LTP induction.

Theta-burst stimuli applied to the LA-BLA synapse, however, reduce the magnitude of LTP by only ~20% (FIG. 3). When slices from hippocampus were taken from the same mice, they demonstrated nearly complete block of LTP. This result indicates that aCaMKII contributes to the induction of LTP in the BLA, but that this contribution is less than that in the hippocampus or possibly that BLA neurons have other means of compensating for the loss of aCaMKII function.

One possible explanation for the unexpectedly small effects of aCaMKII is the close relation between NMDA receptors and CaMKII-mediated LTP. In support of this hypothesis, Giese *et al*.[20] demonstrated that the residual LTP in T286A mutant aCaMKII mice was insensitive to AP5. Because the ratio of NMDA-sensitive to

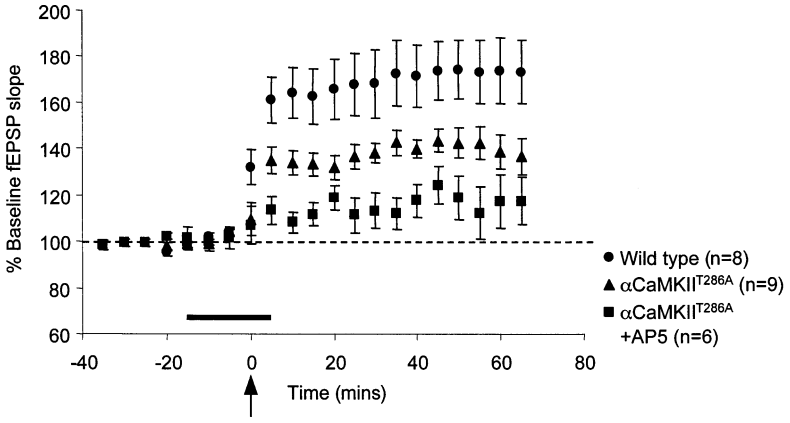

FIGURE 3. The residual LTP in T286A mutants is AP5 sensitive. WT refers to wild-type animals, aCaMKII^{T286A} to T286A homozygous mutant animals, and aCaMKII^{T286A} +AP5 to mutant slices treated with AP5. The *horizontal dashed line* indicates the baseline level (100%). The *thick black line* indicates when AP5 was applied to the MUT+AP5 group. The *arrow* (at time 0) indicates delivery of TBS, and n's refer to number of animals tested.

NMDA-insensitive LTP appears to be lower in BLA than in CA1, it is possible that the residual LTP in T286A represents only VGCC-mediated LTP, in which case NMDA receptor antagonists should have no effect. TBS given to amygdala slices of T286A mutant mice in the presence of 50 M D-AP5, however, led to LTP that was significantly smaller than that in saline control animals (FIG. 3), indicating that some NMDA-dependent LTP is not mediated through aCaMKII, a dramatic difference from CA1 and neocortex.

Transcription Factors and Other Intracellular Signaling Molecules

The induction and early maintenance of LTP may involve the posttranslational modification of proteins by phosphorylation, but these changes would be limited to the life span of the protein and subjected to further modification by phosphatases. For LTP to last longer than a few hours probably requires the synthesis of new proteins. Bridging the gap between calcium influx and the activation of calcium-dependent protein kinases will involve the recruitment of additional cell signaling molecules, including inducible transcription factors that can direct the synthesis of specific proteins.

The most widely studied signaling pathway that could perform this function is the Ras/MAPK/CREB pathway. CREB (cAMP-responsive element binding protein) is a transcription factor that is constitutively bound to the CRE (cAMP-responsive element) site in the promoter region of a variety of genes. When phosphorylated, CREB (and CREB family proteins) can modulate the expression of genes with CRE binding sites.[36] One of the major kinases capable of phosphorylating CREB is mitogen-activated protein kinase (MAPK), itself activated by a complex series of phosphorylations that can be initiated by activated RAS.[37] Thus, extracellular signals that can eventually activate RAS, then MAPK and CREB can influence gene expression.

Numerous studies have indicated that the induction of LTP in the hippocampus and the amygdala results in activation of MAPK family members ERK1 and ERK2 (extracellular-signal regulated kinase 1 and 2, also known as p44 MAPK and p42 MAPK, respectively; reviewed in Ref. 37). Although these studies have indicated that ERK2 is activated more than ERK1, both appear to be phosphorylated by MAP kinase kinase (MEK) in response to both high-frequency stimulation and several forms of learning and memory. MEK itself is activated by Raf, which in turn is activated by Ras, suggesting that Ras activation should follow tetanic stimulation or appropriate forms of learning. Ras activation can be affected through the binding of exchange of GDP for GTP, which is enhanced by activation of RasGRF.[38] Thus, induction of LTP as well as learning and memory should be affected by disruption of RasGRF, Ras, MEK, ERK, or CREB.

Brambilla *et al.*[6] examined LTP in CA1 and BLA *in vitro* in mice with targeted deletion of RasGRF and found that LTP was deficient in the amygdala, but normal in CA1. This was consistent with their behavioral observations that spatial learning (in the water maze and 8-arm radial maze) was normal, whereas fear conditioning (conditioned freezing, passive and active avoidance) was impaired at 24 hours, but not at 30 minutes. This suggests that RasGRF, while present in neurons in both structures, is only required for LTP in BLA. On the other hand, these behavioral results were not duplicated in another RasGRF knockout mouse, a discrepancy that has yet to be resolved.[39]

Inhibition of MAPK activation by application of MEK inhibitors produces deficits in synaptic plasticity and learning in both the hippocampus and the amygdala. Atkins *et al.*[40] found that cued and contextual fear conditioning led to increased phosphoERK1 and phosphoERK2 in the hippocampus and that systemic administration of the MEK inhibitor SL327 blocked activation of ERK1 and ERK2 as well as cued and contextual fear conditioning in a dose-dependent manner. Moreover, application of SL327 to hippocampal slices blocked LTP in rat CA1. Schafe *et al*.[41] extended these findings by reporting that fear conditioning increased the number of neurons that were immunoreactive for phosphorylated MAPK in the lateral amygdala. Long-term, but not short-term, memory for fear conditioning was impaired by systemic application of the MEK inhibitor U0126, which also blocked LTP induction in the lateral amygdala when bath-applied to slices. Thus, MAPK may represent a consensus mechanism for the establishment of long-lasting LTP in CA1 and BLA, perhaps as a final common pathway for activation by CaMKII, PKA, PKC, and PI-3 kinase.[42]

Although ERK1 appears to be less strongly activated than ERK2 during associative learning, examinations of LTP in amygdala, hippocampus, and ventral striatum of mice with targeted deletion of ERK1 may be illuminating. Selcher *et al*.[43] tested fear conditioning and hippocampal LTP in a line of ERK1 knockout mice and found no differences in either the behavioral or the physiological measure, although they did report that mice were more active in the open field. Mazzucchelli *et al*.[44] examined a different line, also resulting in a null mutation of ERK1 while sparing ERK2. In cultured neurons from three different structures (hippocampus, neocortex, and striatum), depolarization with high potassium or activation with extracellular glutamate resulted in five- to sixfold increases in activation of ERK2 in ERK1-deficient tissue, relative to littermate controls. LTP was slightly but significantly reduced in CA1 of ERK1-deficient mice when induced with TBS, but not with 100 Hz tetanus, in agreement with the data of Selcher *et al*.[45] with MEK inhibitors in mice. On the other hand, LTP was not affected at all in BLA and was dramatically and significantly increased in the ventral striatum. Thus, although MAPK may represent an important link in LTP induction and maintenance in more than one forebrain region, it is still unclear whether it plays the same role in each of these structures or which form of MAPK is most important.

CONCLUSIONS

Clearly, the examples presented here only begin to demonstrate the range of mechanisms that can participate in, or significantly modify, synaptic plasticity in the amygdala and the hippocampus. Our intention was to demonstrate that at every level in the cascade of biochemical and molecular events that constitute synaptic plasticity, significant differences exist between two of the most widely studied brain regions. This diversity has significant implications for attempts to clarify the contribution of synaptic plasticity in learning and memory. On the one hand, it could be seen as an impediment. If NMDA receptors were always critical to LTP induction, for example, then local infusion of antagonists or regionally restricted knockout would always block LTP and allow a relatively clear interpretation of the behavioral consequences. Moreover, systemic administration of NMDA antagonists would lead

to similarly uncomplicated results, because we could know that all LTP (and nothing but LTP) had been blocked. This, however, cannot be the case. On the other hand, the fact that blocking NMDA receptors, or VGCC, or ERK1 may have effects that are specific to a particular set of synapses means that these manipulations may, in essence, produce a regionally specific effect on plasticity that will substantially assist interpretation of behavioral results.

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