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Long-Term Potentiation, Protein Kinase C, and Glutamate Receptors

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Contents

Abstract

Among the various molecular events that have been proposed to contribute to the mechanisms of long-term potentiation (LTP), one of the most cited possibilities has been the activation of protein kinase C (PKC). Here we review various aspects of the cellular actions of PKC activationa and inhibition, with special emphasis on the effects of the kinase on synaptic transmission and the *N*-methyl-D-aspartate (NMDA) and non-NMDA receptor-mediated components of synaptic responses. We discuss the implications of these effects for interpretations of the role of PKC in the mechanisms of LTP induction and maintenance.

Index Entries: Plasticity; LTP; hippocampus; synaptic transmission.

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Introduction

Application of trains of high-frequency stimulation to a number of excitatory pathways in the central nervous system (CNS) triggers a cascade of events that results in long-lasting enhancement of the efficacy of synaptic transmission (Bliss and Gardner-Medwin, 1973). The form of plasticity, essentially characterized in hippocampal formation, is usually referred to as long-term potentiation (LTP) and is generally considered one of the possible mechanisms used by the brain for information storage and processing.

Recent advances in the pharmacology of glutamate receptors have made it possible to identify some of the key events implicated in the induction of LTP (Collingridge et al., 1983; Harris et al., 1984). Specifically, it has been shown that during the application of high-frequency trains, two important factors, the summation of the depolarization produced by each pulse and the refractoriness of γ-aminobutyric acid (GABA)-mediated inhibition on consecutive trains contribute to overcome the voltage-dependent blockade by magnesium of the *N*-methyl-D-aspartate (NMDA) receptor-associated channel and allow calcium to enter the postsynaptic spines (Lynch et al., 1983; Nowak et al., 1984; Herron et al., 1986; Larson and Lynch, 1986,1988; Malenka et al., 1988). The main issue now is to understand the biochemical events triggered in postsynaptic spines by this change in calcium concentration and the nature and locus of the long-lasting modifications that are responsible for the potentiation effect.

Several mechanisms have been proposed to account for LTP based on the implication of various second messenger systems and of either pre- or postsynaptic modifications (Madison et al., 1991). Among these possibilities, protein kinase C (PKC), a phospholipid and calcium-dependent kinase, has been frequently cited as a candidate for playing a crucial role in the mechanisms responsible for this form of plasticity. Originally, the idea that the kinase might contribute to LTP was proposed by Akers et al. (1986) based on the observation that translocation of the enzyme to the membrane and phosphorylation of an important presynaptic substrate could be detected following high-frequency stimulation. Malenka et al. (1986b) then reported that PKC activation by phorbol esters produces a long-lasting enhancement of synaptic responses that prevents further potentiation by high-frequency stimulation. Since then, a number of studies have further examined the role of PKC in LTP and come to different,sometimes contradictory conclusions. A difficulty in analyzing the contribution of the kinase to mechanisms of plasticity results from the involvement of the enzyme in various aspects of cellular physiology. There are a number of reports describing the interactions of PKC with different types of ionic channels (Kaczmarek, 1987).

In the present article, we summarize some of the most important cellular actions of PKC activation or inhibition in hippocampal neurons and discuss the implications of these effects for the mechanisms of LTP. The general picture that emerges from this analysis is consistent with the idea that PKC is not directly implicated in the mechanisms responsible for the change in synaptic efficacy but that the enzyme could participate in the control and modulation of the events involved in LTP induction.

Steps of LTP

There are many ways that an enzyme such as PKC can interact with or contribute to the mechanisms of LTP. For reasons of clarity, it is important to distinguish between different phases in the cascade of events that are involved in the changes in synaptic efficacy. It is now widely accepted that during episodes of high-frequency stimulation, the major event is a calcium influx in the postsynaptic spines through NMDA receptor-associated channels (*see* Collingridge and Singer, 1990). All mechanisms susceptible to interference with the magnitude of this change in calcium concentration in the postsynaptic spines will thus be said to interact with the induction phase.

This change in calcium concentration in the postsynaptic spines is then likely to activate a number of calcium-sensitive second messengers or enzymes, among which is PKC. These can be only transiently active and promote the production of more stable modifications. These events belong to what will be referred to as an intermediary phase. The increase in synaptic efficacy observed hours or even days after the episode of high-frequency stimulation (Staubli and Lynch, 1987), must be related to stable modifications in either the pre- or postsynaptic compartments. The mechanisms responsible for these long-lasting changes are said to mediate LTP expression and are involved in the maintenance phase of this form of plasticity. PKC has been proposed to contribute to or interact with LTP at all of these different steps. We will thus consider in turn the role of the enzyme in these three phases.

Cellular Actions of PKC

Before discussing the interactions among activation or inhibition of PKC and the different phases of LTP, it is important to summarize some of the major cellular actions of the enzyme. Application of phorbol esters to hippocampal slices results in the closure of a number of ionic channels. Chloride, potassium, and calcium currents have all been reported to be reduced or blocked in the presence of the drug. The chloride conductances that are blocked by phorbol esters could be essentially located on dendrites and thus affect signal transduction between spines and soma (Madison et al., 1986). A number of potassium currents are also depressed. These include a persistent potassium current and the calcium-activated potassium current that contributes to the slow after hyperpolarization (Baraban et al., 1985; Malenka et al., 1986a; Storm, 1987). The transient potassium current Ia does not seem, however, to be affected in hippocampal neurons (Doerner et al., 1988). The depressant action of phorbol ester on these potassium conductances may thus considerably influence neuronal excitability. Activation of the kinase also results in the inhibition of N and L types of calcium currents, an action that may affect calcium dynamics in postsynaptic dendrites (Doerner et al., 1988,1990).

PKC and Synaptic Transmission

Phorbol esters as well as diacylglycerol applied to hippocampal slices result in a considerable enhancement of synaptic responses, the effect varying between 120–150% (Malenka et al., 1986b; Muller et al., 1988). Several observations support the idea that this potentiation is essentially the result of a presynaptic action of PKC, involving increased release probability. The frequency of spontaneous inhibitory and excitatory potentials was shown to be increased, as was the release of glutamate in the superfusion medium (Malenka et al., 1987). In contrast, phorbol esters do not modify the sensitivity to ionophoretically applied glutamate (Malenka et al., 1986b; Segal, 1989). Increased release has also been shown for various neurotransmitters or neurohormones in different areas of the CNS, as well as in synaptosomes (Zurgil and Zisapel, 1985; Kaczmarek, 1987; Finch and Jackson, 1990). At the neuromuscular junction, analyses of quantal properties indicate that the effect is the result of an increase in the probability of transmitter release as opposed to a larger size of quantal packages (Shapira et al., 1987). One way in which phorbol esters might enhance release probabilities is through modifications of calcium dynamics in presynaptic terminals. Since PKC is involved in the control of many ionic channels and broadens action potentials by blocking potassium channels, it has been proposed that this might enhance calcium entry in the presynaptic terminals during action potentials (Storm, 1987). Another possibility is that PKC acts by directly enhancing presynaptic calcium currents, similar to what has been described in Aplysia neurons, or by affecting the release mechanisms (DeRiemer et al., 1985).

A postsynaptic involvement of the kinase has also been proposed to contribute to the enhance-

ment of synaptic responses (Hu et al., 1987). The effects that were observed, however, could also be interpreted as resulting from the action of the enzyme on postsynaptic conductances and more specifically, on the closure of dendritic chloride conductances and potassium currents (Baraban et al., 1985; Madison et al, 1986; Malenka et al., 1986a). These effects may well contribute to enhancing signal transduction from dendrites to soma, but they probably do not account for the synapse-specific potentiation that characterizes LTP (Chavez-Noriega et al., 1990).

PKC and LTP Induction Mechanisms

High-frequency stimulation applied in the presence of phorbol esters generates a significantly smaller degree of potentiation than in control conditions. Since phorbol esters also enhance synaptic responses, it had been proposed that the potentiation effect produced by phorbol esters might be similar to that produced by high-frequency stimulation and therefore, that PKC activation occludes LTP (Malenka et al., 1986b). An alternative interpretation, however, is that phorbol ester treatment interferes with LTP induction mechanisms. In support of this interpretation is the observation that the summation of synaptic responses within high-frequency trains is considerably reduced by the drug (Muller et al., 1988). More recently, a reduction in the NMDA component of responses to burst stimulation was also demonstrated (Fig. 1; Muller et al., 1990). It is likely that this effect was not the result of a direct action of PKC or phorbol esters on NMDA currents but rather resulted from indirect mechanisms such as the reduction in short-term forms of plasticity and the enhancement in inhibitory GABA-ergic transmission that is observed following phorbol ester treatment (Gustafsson et al., 1988; Muller et al., 1988; Turnbull et al., 1988). GABA-ergic inhibition in several respects has been shown to play an important role in the control and modulation of LTP induction (Larson and Lynch, 1986; Davies et al., 1991). An additional aspect is that PKC activation results in a considerable attenuation of calcium currents in hippocampal pyramidal neurons (Doerner et al., 1988). Although the contribution of these calcium currents to LTP induction mechanisms is not precisely known, they might participate in some way, since recent results indicate that LTP can be obtained using specific patterns of afferent stimulation in the presence of an NMDA recep-tor antagonist (Grover and Teyler, 1990). Phorbol esters also interact with phosphoinositide hydrolysis induced by excitatory amino acids, another factor that might contribute to the changes in calcium concentrations that occur during the induction phase (Schoepp and Johnson, 1988).

If activation of the kinase has been reported to interfere with induction mechanisms, inhibition of the enzyme might also produce the same effect. A reduction in the NMDA component of responses to burst stimulation was observed following H-7 treatment, a poorly selective antagonist of the kinase (Fig. 1; Muller et al., 1990). We have also observed a similar effect, although less marked, following treatment with stauro-sporine, a considerably more potent antagonist of the catalytic subunit of the kinase (Muller et al., in press). In the case of H-7, a recent study indicates that this effect is probably partly related to a direct interaction of the drug with the NMDA receptor-associated channel (Amador and Dani, 1991). It is, however, also possible that NMDA receptors can be modulated by phosphorylation: A progressive disappearance of NMDA-mediated currents was reported in intracellular recordings in which adenosine triphosphate (ATP) or other energy-rich compounds had not been added in the pipet solution (MacDonald et al., 1989). Thus, there are a number of indications that suggest that phorbol ester treatment and PKC antagonists might interfere with induction mechanisms.

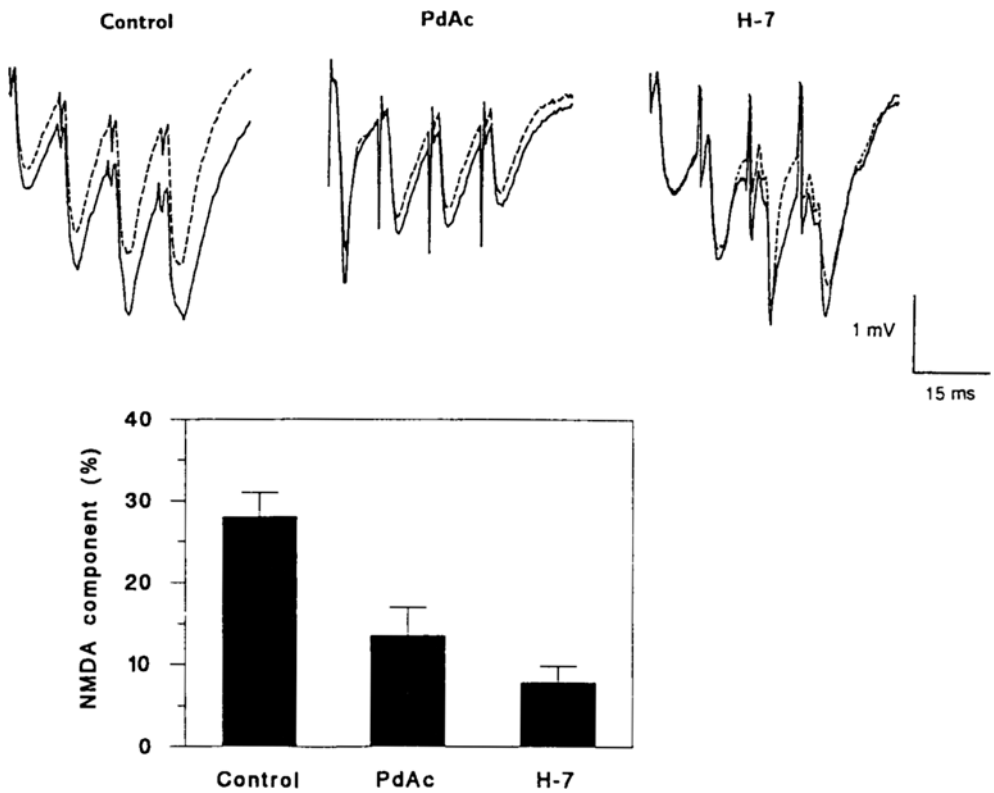

Fig. 1. Interaction of PKC with LTP induction mechanisms. Illustration of synaptic responses to burst stimulation recorded before (solid line) and after (dashed line) application of 50 μ*M* D-AP5 in either control conditions (0.1 m*M* Mg in the medium), in the presence of phorbol diacetate (10 μ*M*), or H-7 (400 μ*M*). Both activation and inhibition of PKC can result in a reduction of NMDA receptor-mediated currents.

Role for Transient Activation of PKC in LTP

Two major observations have been interpreted as supporting a role for a transient activation of PKC in LTP. First, the synaptic enhancement produced by phorbol esters was reported to be long-lasting, and thus, a transient activation of PKC might result in LTP (Malenka et al., 1986b). Later studies, however, showed that the effect is only transient, the duration of the synaptic enhancement being directly related to the lipophilicity of the compounds that are used (Fig. 2; Malinow et al., 1988; Muller et al., 1988). Reversibility of the effects of the kinase was also observed concerning its action on ionic channels (Baraban et al., 1985; Doerner et al., 1988). It follows then that the phosphorylation activity of the kinase is probably counteracted by that of phosphatases and therefore, that a transient phosphorylation of specific proteins can hardly be responsible for long-lasting synaptic modifications. The same observation also indicates that a selective and transient activation of the kinase cannot be sufficient to produce LTP: If the kinase is implicated, other mechanisms will also be required.

Another piece of evidence compatible with the idea of a transient activation of PKC in LTP comes from a number of studies showing that antagonists of the enzyme interfere with LTP mechanisms: i.e., in their presence, high-frequency stimulation results in a decaying form of poten-

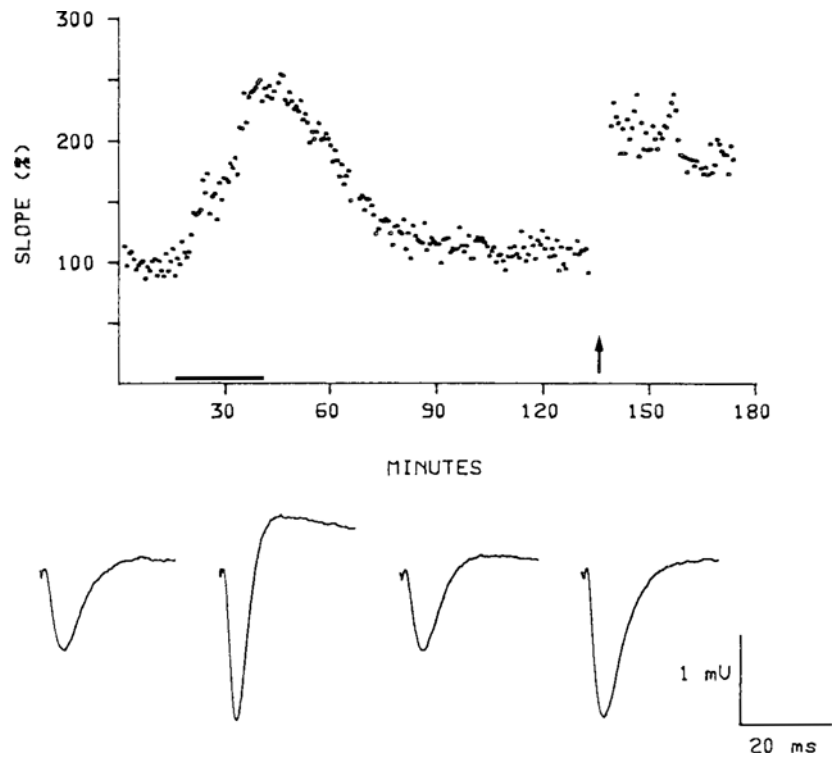

Fig. 2. A transient activation of PKC by phorbol diacetate does not result in long-lasting enhancement of synaptic responses. After washout of phorbol diacetate, the amplitude of dendritic potentials returned to baseline values, and high-frequency stimulation still induced LTP.

tiation. The effect was observed as well with non-selective and relatively weak antagonists, such as polymixine B, H-7, and sphingosine as with more recent and potent compounds, such as staurosporine, K252-b, or other specific peptides (Lovinger et al., 1987; Malinow et al., 1988; Reymann et al., 1988; Malenka et al., 1989; Manilow, 1989; Denny et al., 1990; Reymann et al., 1990). Although these results suggest that a transient PKC activation might play an important role in LTP, they can also be accounted for in a different way. It should be noted that translocation of the enzyme to the membrane was not observed shortly after high-frequency stimulation (Akers et al., 1986). Also, the decaying form of potentiation recorded in the presence of PKC antagonists could result from an interaction with induction mechanisms. A recent study concluded that the duration of the synaptic enhancement is controlled by postsynaptic factors such as the magnitude and duration of the changes in calcium concentration in postsynaptic spines (Malenka, 1991). As mentioned above, there is evidence that two PKC antagonists, H-7 and staurosporine, reduce NMDA receptor-mediated components of responses to burst stimulation (Muller et al., 1990). In addition, in the presence of staurosporine, coactivation of two pathways during the application of high-frequency trains is able to transform the decaying form of potentiation into robust LTP (Muller et al., in press). It is possible, therefore, that the decaying potentiation observed following treatments with PKC antagonists reflects an interaction of the kinase with the mechanisms that control calcium dynamics during the induction phase rather than a role of the enzyme in triggering longer-lasting modifications.

Role of PKC in the Maintenance Phase of LTP

One of the most favored ideas concerning an implication of PKC in LTP has been the possibility that the kinase is directly involved in the long-lasting modifications that underlie the potentiation effect (Linden and Routtenberg, 1989). As already discussed, a transient phosphorylation activity is unlikely to result in long-lasting changes. It has thus been proposed, to account for long-term effects, that the kinase could remain active for a long period of time (Malinow et al., 1988). This could be achieved through the action of calcium-activated proteases, such as calpain, that can cleave the enzyme into a constitutively active form called protein kinase M (Pontremoli et al., 1986). Calpain is present in hippocampal neurons and has also been implicated in LTP (Lynch and Baudry, 1984; Staubli et al., 1988; Del Cerro et al., 1990).

There are a number of observations that are consistent with or support this possibility. PKC activation does result in a synaptic enhancement; and if the kinase activity is sustained, then this could account for LTP. Translocation of the kinase to the membrane and phosphorylation of a specific substrate of PKC, a protein referred to as F1, B50, or GAP-43, have been reported following high-frequency stimulation (Akers et al., 1986; Lovinger et al., 1986; Linden and Routtenberg, 1989).

Translocation of the kinase was detected 60 min but not 1 min after stimulation, and the phosphorylation was reported to last for 3 days. Antagonists of PKC not only have been shown to interfere with LTP induction, but also, in the case of H-7, the drug was reported to reversibly eliminate the maintenance phase of LTP (Malinow et al., 1988).

There are, however, other results that are at variance with this interpretation. Discrepancies concern essentially two aspects: the similarity between the synaptic enhancement produced by phorbol esters and LTP and the effect of PKC antagonists on preestablished LTP.

Phorbol Ester-Induced Synaptic Enhancement and LTP

There are a number of differences that distinguish the synaptic enhancement produced by phorbol esters and the long-lasting potentiation produced by application of high-frequency stimulation. A first aspect concerns the type of synapses that express both forms of potentiation. Whereas phorbol esters enhance the release of various neurotransmitters in many different areas of the CNS and the peripheral nervous system (PNS), including neuromuscular junctions (*see above*), LTP is expressed only by specific types of synapses. Second, if LTP and the synaptic enhancement produced by phorbol esters were the result of common mechanisms, an occlusion of the effect of one by the other would be expected. If this is partially true in the case of the occlusion of LTP by phorbol ester treatment, i.e., LTP can hardly be induced in the presence of phorbol esters (Malenka et al., 1986b), then the reverse is not (Fig. 3). Two studies concluded that the enhancement produced by phorbol esters is not reduced by prior induction of LTP (Gustafsson et al., 1988; Muller et al., 1990).

In addition phorbol ester treatment, similar to all other manipulations that enhance release probabilities, is accompanied by a reduction in the degree of paired-pulse or frequency facilitation, a short-term form of plasticity well characterized at peripheral synapses (Gustafsson et al., 1988; Muller et al., 1988; Zucker, 1973). In contrast, LTP induction in area CA1 does not modify the ratio of facilitation and does not affect the calcium sensitivity of release (Muller and Lynch, 1989).

Finally, the synaptic enhancement produced by phorbol esters, similar to paired-pulse or frequency facilitation, is expressed as well as or even to a higher degree by NMDA as compared to AMPA receptors, whereas a very different situation is found following LTP (Fig. 4; Muller and Lynch, 1990). Using different approaches to measure the contribution of the two classes of recep-

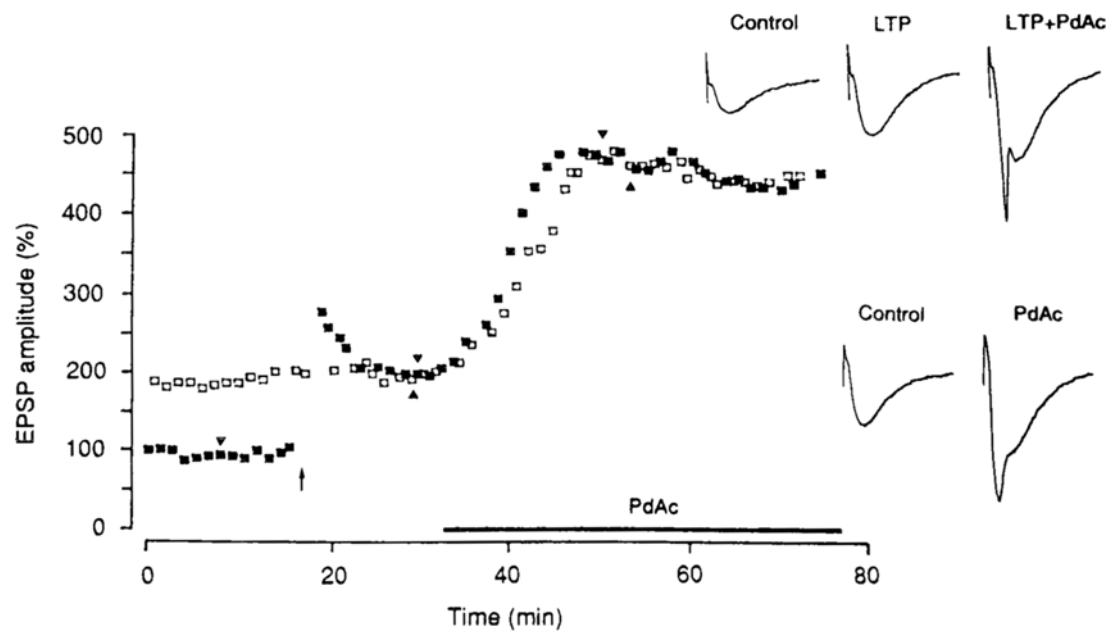

Fig. 3. Prior induction of LTP does not reduce the magnitude of the synaptic enhancement produced by phorbol esters. Two stimulating electrodes were placed in area CA1, and LTP generated on one of them. Application of phorbol diacetate then enhanced to the same degree potentiated and control responses. LTP, thus, does not occlude the effect of PKC activation.

tors to LTP a constant finding has been that NMDA receptors contribute very little to the potentiation effect or at least considerably less than AMPA receptors (Fig. 4; Kauer et al., 1988; Muller et al., 1988; Muller and Lynch, 1988). Taken together, these discrepancies strongly suggest that the mechanisms responsible for both forms of potentiation (phorbol ester-induced synaptic enhancement and LTP) are different.

Effects of PKC Antagonists on the Maintenance Phase of LTP

Another controversial issue concerning the role of PKC in LTP expression mechanisms is related to the effects of PKC antagonists on preestablished potentiation. If indeed a sustained PKC activity is responsible for LTP, then blockade of the catalytic subunit of the enzyme should eliminate the potentiation effect. Using high concentrations of H-7, a rather nonselective antagonist of PKC, Malinow et al. (1989) reported that the drug reversibly abolished preestablished LTP. In another series of studies, however, we observed that H-7 did reduce the size of potentiated responses, but the drug affected in the same way control potentials. Comparing the effects of H-7 on naive and potentiated pathways, we have been unable to detect any significant reduction of the potentiation effect (Muller et al., 1990). The same issue has also been addressed in other studies using more recent and potent angonists of the catalytic subunit, such as staurosporine or K252-b (Reymann et al., 1990; Denny et al., 1990; *see* Fig. 5). Evidence has been obtained that the drugs penetrate into the cells and/or interfere with sub-

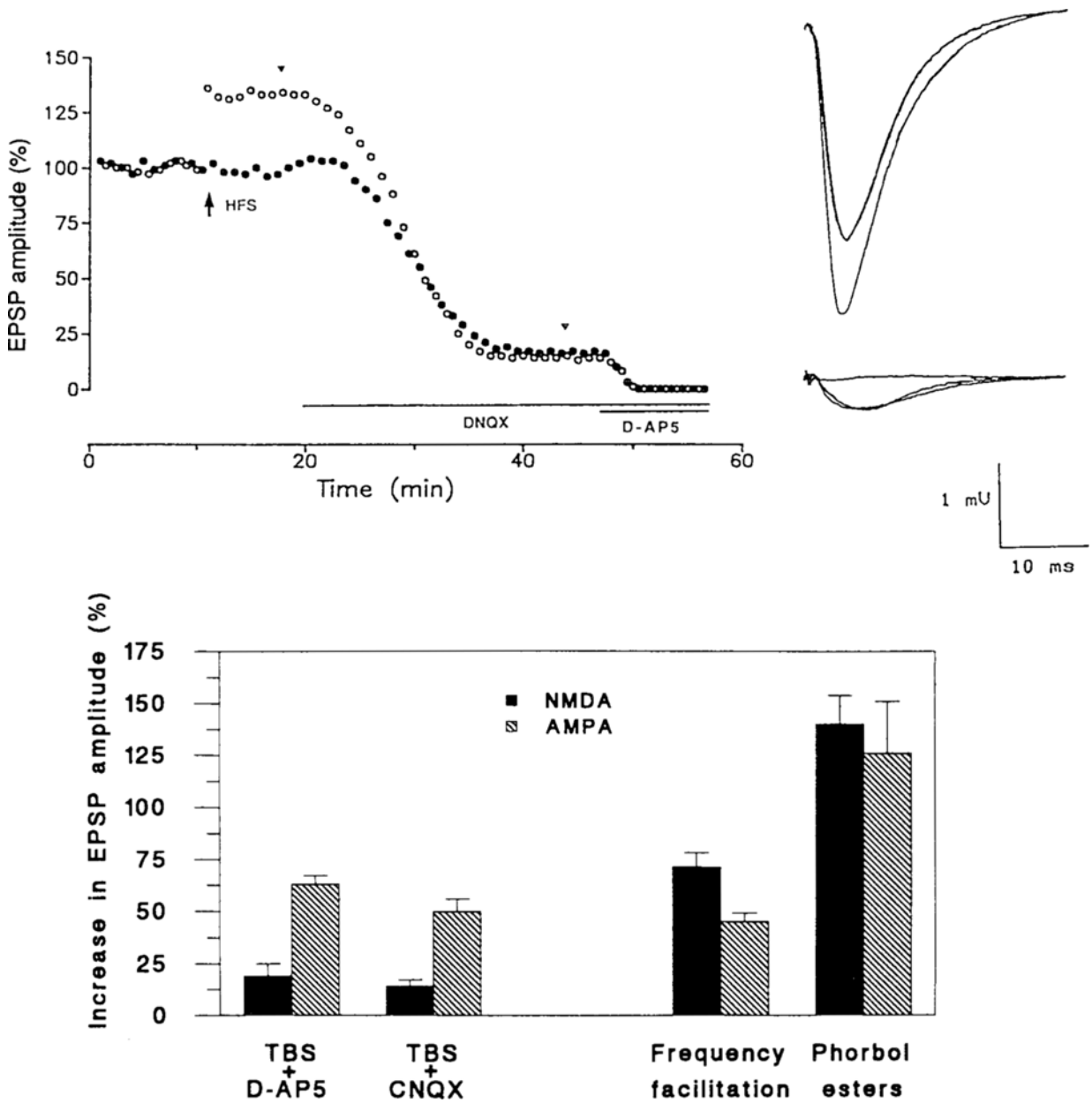

Fig. 4. The maintenance phase of LTP is essentially expressed by AMPA vs NMDA receptor-mediated components, whereas frequency facilitation or phorbol esters enhance more or at least to the same degree NMDA as compared to AMPA receptor-mediated responses. The contribution of the two types of receptors to LTP was measured by comparing responses recorded before or after theta burst stimulation (TBS) and application of either an NMDA receptor antagonist (D-AP5) or a blocker of AMPA receptors (CNQX; Muller and Lynch, 1988; Muller et al., 1988). The values concerning frequency facilitation were obtained by application of D-AP5 (Muller and Lynch, 1990), whereas the effects of phorbol esters were compared in the presence or absence of CNQX.

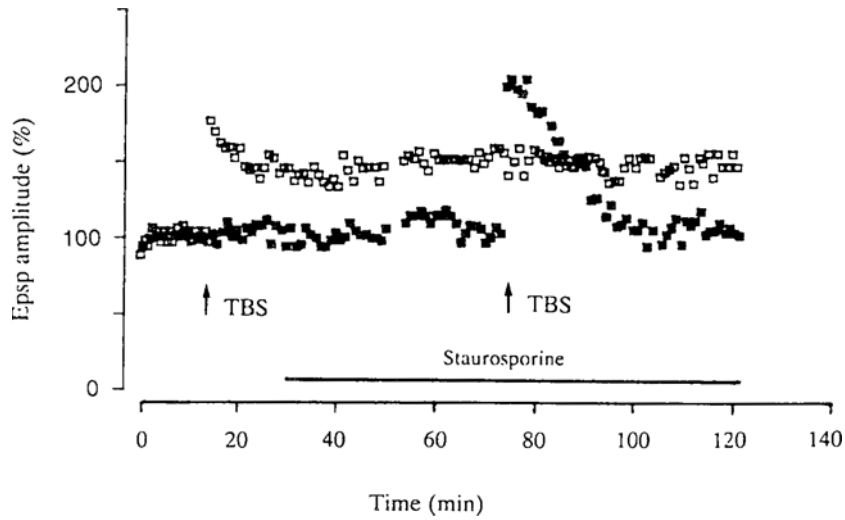

Fig. 5. Antagonists of the catalytic subunit of PKC do not affect preestablished LTP but interfere with induction mechanisms. This is an illustration of an experiment in which synaptic responses were elicited on two pathways. Theta burst stimulation (TBS) on one input (arrow) results in robust LTP that is not modified by 10 μM staurosporine. However, TBS stimulation applied to the second input in the presence of the PKC antagonist generates only a decaying form of potentiation.

sequent induction of LTP, but in all studies, no effect on pre-established LTP was observed (Fig. 5). It should be noted also that specific peptides that selectively block PKC or Cam kinase II do not abolish preestablished LTP when injected in postsynaptic neurons (Malinow et al., 1989; Malenka et al., 1989). Considering all these results, it thus seems reasonable to conclude that a sustained activity of PKC does not underlie LTP.

Conclusion

When applying high-frequency trains to a group of afferents, substantial changes in the intracellular calcium concentration probably occur in the postsynaptic spines and the presynaptic terminals. It is likely, therefore, that calcium-sensitive second messenger systems will be activated (Williams and Bliss, 1988; Lynch et al., 1989; Goh and Pennefather, 1989) and that translocation of PKC to the membrane will take place (Akers et al., 1986; Baskys et al., 1990). The real issue, however, is to understand the precise physiological role of these second messengers in the production of stable synaptic modifications.

The data that have been reviewed here can be summarized to propose the following picture concerning the role of PKC in LTP. Presynaptically, activation of the kinase enhances transmitter release probably by modifying the calcium dynamics in the terminals (Shapira et al., 1987). The effect could result from interactions with ionic channels, such as a blockade of potassium currents and a broadening of action potentials (Storm, 1987). This modulatory influence of PKC on release is probably expressed nonspecifically in all types of synapses, excitatory and inhibitory.

The enhancement of inhibition in hippocampus as well as the reduction in short-term forms of plasticity probably accounts in part for the reduced summation of excitatory potentials during high-frequency trains, the reduction of the NMDA components of responses to burst stimulation, and the difficulty of producing LTP in the presence of phorbol esters (Malenka et al., 1986b; Gustafsson et al., 1988; Muller et al., 1988; Turnbull et al., 1988; Muller et al., 1990).

In postsynaptic neurons, activation of PKC also affects a number of ionic channels and more specifically, results in a closure of dendritic chloride conductances (Madison et al., 1986), a closure of potassium and calcium-activated potassium channels (Baraban et al., 1985; Malenka et al., 1986a; Storm, 1987), and a reduction of calcium currents (Doerner et al., 1988). These actions of PKC might contribute to LTP by enhancing signal transduction from dendrite to soma (Hu et al., 1987), but most likely, they do not account for the synapse-specific changes in transmission efficacy. At the level of postsynaptic dendrites or spines, PKC might also interact with calcium dynamics during trains of high-frequency stimulation. This could occur either through a direct modulation of NMDA receptors or via indirect actions on other ionic channels (Doerner et al., 1988; Muller at al., 1988; MacDonald et al., 1989; Grover and Teyler, 1990). These effects of the kinase could thus explain the decaying form of potentiation that is observed when LTP is induced in the presence of PKC antagonists (Malenka, 1991).

Whether a transient activation of PKC also participates in the generation of the stable modifications that will be responsible for the change in synaptic efficacy is still unclear. There is at least no strong evidence that this might be the case, since the effect of PKC antagonists can also be interpreted as resulting from effects of the kinase on LTP induction mechanisms. In any case, if a transient activation of PKC is involved in LTP, it is not by itself a sufficient step to generate LTP. Other mechanisms should also contribute to this phase, since activation of the kinase by phorbol esters does not result in long-lasting modifications (Muller et al., 1988).

Finally, the differences reported between the synaptic enhancement produced by phorbol esters and LTP and the absence of selective blockade of preestablished LTP by PKC antagonists strongly suggest that the maintenance phase of LTP does not require sustained PKC activity (Gustafsson et al., 1988; Muller et al., 1988,1990; Reymann et al., 1990). In summary, the most recent evidence supports the idea that PKC might be involved in the control of LTP induction mechanisms but does not participate in its expression.

Acknowledgments

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