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Extracellular ATP as a neurotransmitter: its role in synaptic plasticity in the hippocampus

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Review

Abstract. Growing evidence indicates that ATP may play a very important role in Long-Term Potentiation (LTP), a neurophysiological process that has been implicated in memory formation. LTP is an enhancement of synaptic strength induced by a specific pattern of high frequency stimulation, or by application of exogenous ATP. In the hippocampus LTP-inducing stimulation is accompanied by a massive, Ca^{2+}-dependent release of ATP from presynaptic terminals. Released extracellular ATP may either interact with numerous types of ATP receptors present on the neuronal surface, or serve as a substrate for ecto-protein phosphorylation. The results of combined electrophysiological and biochemical experiments indicate that participation of extracellular ATP in the ecto-protein phosphorylation process is most likely involved in the permanent amplification of the synaptic response in the hippocampus.

Key words: ATP, neurotransmission, LTP, hippocampus

ATP AS A NEUROTRANSMITTER

Since the first demonstration of stimulation-dependent release of ATP from the nervous tissue (Holton 1959), there is growing interest in the role of ATP in synaptic transmission (Phillis and Wu 1981, Burnstock and Kennedy 1985, Burnstock 1990, Nishimura et al. 1990). ATP is stored in the nerve terminals and coreleased with several neurotransmitters in different biological preparations in a Ca^{2+}-dependent way (Phillis and Wu 1981). In most of the preparations the release of ATP was not abolished by antagonists of postsynaptic receptors indicating presynaptic release of ATP (Phillis and Wu 1981, Burnstock 1990). Released, extracellular ATP can be quickly hydrolyzed by a chain of ectonucleotidases (Kreutzber et al. 1986, Nagy et al. 1986) and products of its hydrolysis (ADP, AMP, adenosine) can influence neurones excitability interacting with specific receptors (Phillis and Wu 1981, Kreutzber et al. 1986). Two types of purinergic receptors (Pl and P2) are presently recognized (Burnstock and Kennedy 1985). Type P1 is more sensitive to adenosine and AMP then to ATP and ADP. Type P2 is less sensitive to adenosine and AMP and more sensitive to ATP, ADP and nonhydrolyzable analogs of ATP (Burnstock and Kennedy 1985). According to the latest research P2 receptors can be further classified into several different subtypes connected with ligand-gated ion channels (O'Connor et al. 1991), or coupled to G proteins (Illes and Nörenberg 1993, Barnard et al. 1994). Activation of P2 receptors stimulates production of D-myo-inositol 1,4,5-triphosphate (IP3) (Pearce et al. 1989) and triggers the release of arachidonic acid from astrocytes through mobilization of intracellular Ca^{2+} and subsequent activation of phospholipase A2 (Bruner and Murphy 1990). ATP can release Ca^{2+} from internal stores in PC12 cells interacting with two functionally distinct population of purinergic receptors (Barry and Cheek 1994). Activation of nucleotide receptor which could be activated by ATP and UTP, stimulated subthreshold release of Ca^{2+}, which was unable to trigger neurotransmitter secretion (Barry and Cheek 1994). However, the activation of independently regulated ionic channel, which could be activated by ATP only, stimulated secretion, because in this case the Ca^{2+} concentration was sufficiently elevated (Barry and Cheek 1994). These results have very important implications for a role of extracellular ATP as a modulator of transmitter release triggered by other stimuli. Released ATP can be also a substrate for ectokinases. Their presence on the surface of neuronal cells was described for the first time by Ehrlich (Ehrlich et al. 1986a,b). Phosphorylation of the surface proteins with extracellular ATP, released during enhanced neuronal activity can be a very powerful signal for long-lasting changes in synaptic efficiency (Ehrlich et al. 1986a,b, Ehrlich 1987, Zhang et al. 1988, Wieraszko and Seyfried 1989a, Wieraszko and Ehrlich 1994, Fuji et al. 1995a,b Chen et al. 1996). Depending on the concentration used, exogenous ATP can exert different effects on cell properties. ATP at micromolar concentration can facilitate calcium influx into smooth muscle through receptor-operated channels (Benham and Tsien 1987) and can increase free calcium levels in cultured nerve cells (Ehrlich et al. 1986a) and chick myotubes (Maggblad and Heilbronn 1988). Electrophysiological studies show that micromolar concentrations of ATP can depress evoked responses in the lateral olfactory tract (Scholfield 1978), but have strong excitatory action on embryonic chick muscle (Hume and Honig 1986) and on rat dorsal horn neurones (Jahr and Jessel 1983). At concentrations above 200 μM ATP and its analogs evoked transient hyperpolarization of mouse fibroblast through increased K^+ permeability (Okada et al. 1984). At mM concentrations ATP can markedly increase intracellular calcium levels in rat parotid cells (McMillan et al. 1987) and in cardiac myocytes (DeYoung and Scarpa 1987, Maggblad and Heilbronn 1988). Recently, for the first time, ATP-mediated, fast synaptic currents have been recorded from neurones of the central nervous system (Edwards et al. 1992, Evans et al. 1992). Thus, one can assume that extracellular ATP is a powerful neuromodulator of cell excitability and may be involved in modulation of synaptic efficiency.

MECHANISMS REGULATING SYNAPTIC EFFICIENCY

There are several chemical and electrical manipulations which can change synaptic efficiency (Bliss and Lomo 1973, Turner et al. 1982, Aniksztejn and Ben-Ari 1991, Madison et al. 1991, Morris et al. 1991). One of the most popular ways to enhance synaptic strength is by a specific pattern of high frequency, electrical stimulation. This permanent, electrically-induced enhancement of the synaptic efficiency, called Long-Term Potentiation (LTP) was for the first time described in the pathways of the mammalian hippocampus which use glutamate as a neurotransmitter (Bliss and Lomo 1973). As some of the mechanisms participating in LTP may be also involved in ATP-induced modulation of synaptic strength, a brief description of the mechanism of LTP will be given. Two forms of synaptic enhancement have been distinguished on the basis of its duration. One form represents a short-lasting (2-5 min) enhancement of the synaptic efficiency that is called posttetanic potentiation (PTP). It overlaps in time with an increase in presynaptic Ca^{2+} levels (Zucker 1989) and may be considered as the induction phase of LTP (Muller et al. 1991), although the mechanisms responsible for these two forms of synaptic plasticity may differ (McNaughton 1982). In contrast to PTP, a nondecremental increase in the synaptic efficiency lasting several minutes to hours is generally recognized as the maintaining phase of LTP (Muller et al. 1991). LTP has been observed in several pathways of the brain and there is growing evidence that this form of synaptic plasticity underlies some forms of memory (Teyler and DiScenna 1987, Soumure-Mourat and Roman 1991). The rise in intracellular Ca^{2+} level which can occur by activation of glutamate receptors of the N-methyl-D-aspartate (NMDA) type (Collingdridge 1988) is essential for induction of nondecremental LTP (Lynch et al. 1983, Morris et al. 1991).

The activation of glutamate receptors is an event considered to be necessary, though not sufficient for the induction of LTP in the hippocampus (Kauer et al. 1988, Morris et al. 1991, Soumireu-Mourat and Roman 1991). Thus, additional, still unidentified factor(s) other than glutamate, must be involved in the mechanism of LTP. Among a variety of 5 molecules, arachidonic acid (Bliss et al. 1991), nitric oxide (Bohme et al. 1991, Mizutani et al. 1993), platelet activating factor (Wieraszko et al. 1993) and extracellular ATP (Wieraszko et al. 1989, Wieraszko and Seyfred 1989a,b, Nishimura et al. 1990, Wieraszko and Seyfried 1990, Wieraszko and Ehrlich 1994, Fujii et al. 1995a,b) seem to be the most likely candidates to act as additional neuromodulators operating in LTP. In the following section the evidence suggesting the involvement of ATP in the mechanism of LTP in mammalian hippocampus will be discussed.

THE ROLE OF EXTRACELLULAR ATP IN HIPPOCAMPAL LTP

In order to exert its effect as a neurotransmitter ATP must be first released to the extracellular space. Indeed, release following electrical or chemical stimulation is a basic criterion for recognizing a compound as a neurotransmitter (Orrego 1979). In 1978 White (White 1978) demonstrated a potassium-induced release of ATP from brain synaptosomes. Using a cortical cup technique, Wu and Phillis (1978) found a 30-fold increase in the release of ATP from rat sensory-motor cortex following electrical stimulation. To minimize the problem of ATP hydrolysis by extracellular Ca^{2+}-ATPase, a photomultiplier was used to monitor directly the release of ATP from Torpedo Marmorata electric organ (Israel et al. 1976). We have modified this technique to detect and quantitate the release of ATP from electrically stimulated hippocampal slices (Wieraszko et al. 1989). Figure 1A depicts the diagram of mammalian hippocampal slice and Fig. 1B shows the apparatus used in this study. Hippocampal slices were placed in the recording chamber mounted over a photomultiplier that was inside a metal block. The slice chamber was made of transparent plastic. The photomultiplier was connected to the pen recorder and the movement of the pen was

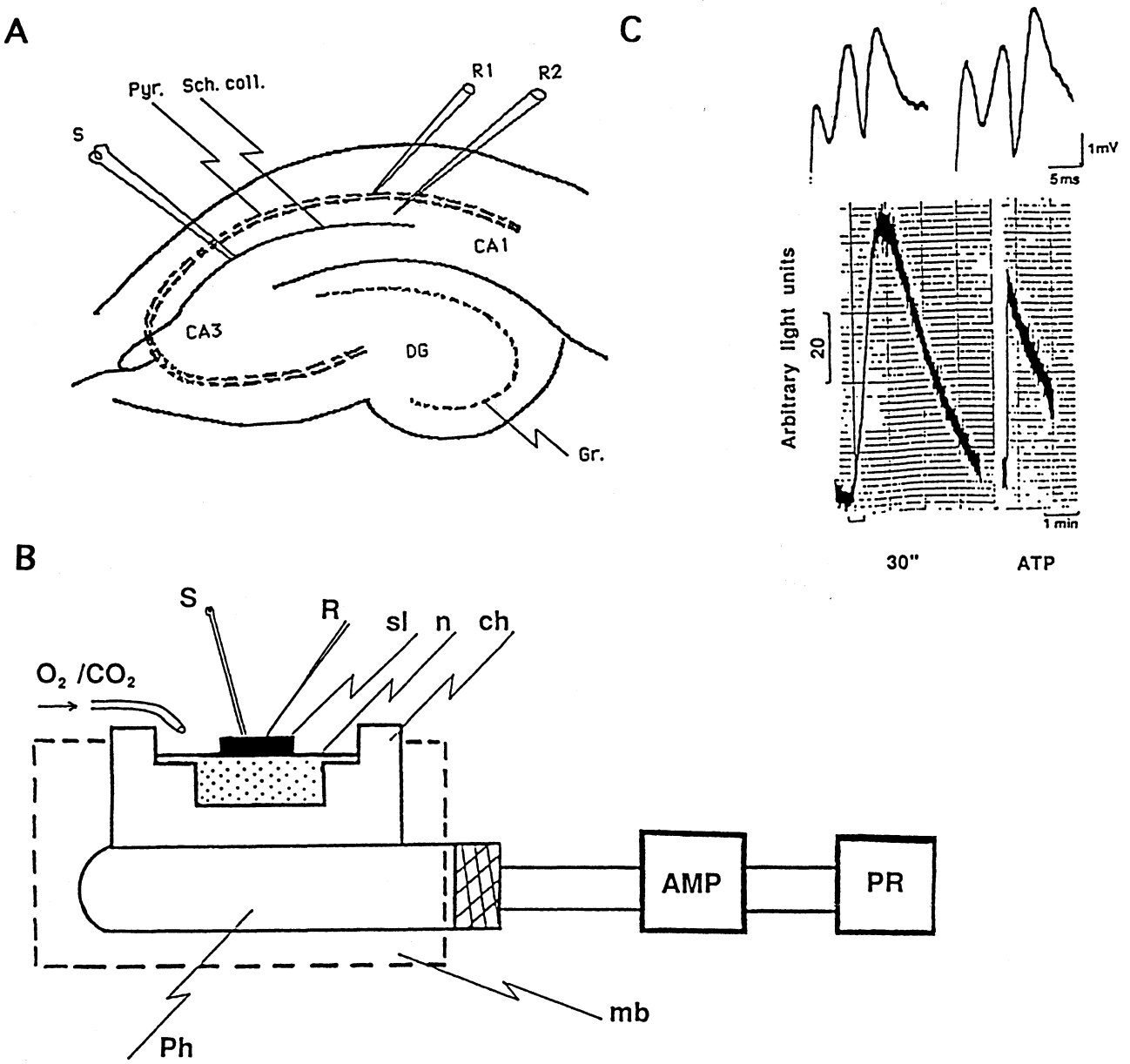

Fig. 1. The experimental design used to evaluate the release of ATP from mammalian hippocampal slices. A, the diagram of hippocampal slice; Pyr., pyramidal cell layer; Gr., granular cell layer; S, stimulating electrode placed on Schaffer collaterals (Sch. coll.); R1 and R2, extracellular, recording electrodes placed on the pyramidal cell layer (to record the population spike) and in stratum radiatum (to record EPSP), respectively; DG, dentate gyrus; CA1 and CA3, hippocampal fields; B, the apparatus for estimating ATP release from hippocampal slices. A slice (sl) is shown on a net (n) in the transparent slice chamber (ch). The slice is immersed in 0.8 ml of buffer containing luciferin-luciferase solution. The chamber fits into an opening in the metal block (mb) containing the photomultiplier (Ph). The light generated travels through the bottom of the chamber to the photomultiplier. After amplification (Amp), the light-induced signal is recorded by the pen recorder (PR). S and R represent stimulating and recording electrodes, respectively. The slice is oxygenated by a tube supplying a mixture of CO_2/O_2 (5%/95%). The entire apparatus is enclosed in a light-tight Faraday cage; C, examples of ATP release from mouse hippocampal slices. Upper traces demonstrate the population spikes recorded before (left) and after (right) application of HFS which induced LTP. Lower traces show the amount of light generated during 30 s (30") application of HFS and following injection of the standard ATP solution (5.5×10^{-10} M). B and C reproduced from Wieraszko et al. (1989) with kind permission of the publisher.

proportional to the amount of light generated in the chamber. The determination of the amount of released ATP was performed using luciferin-luciferase system. The stimulating and recording electrodes were placed on Schaffer collaterals and in the pyramidal cell layer respectively. As shown in Fig. 1C, high frequency stimulation (300 Hz for 50 ms at 2 s intervals for a total of 30 s) evokes ATP release. Simultaneous recording of evoked potentials revealed that the pattern of stimulation which triggered release of ATP also induced LTP. Omitting calcium from the incubation medium eliminated ATP release and blocking postsynaptic glutamate receptors with 2 mM kynurenic acid had no influence on ATP release (Wieraszko et al. 1989). These data demonstrate that ATP can be released from stimulated hippocampal nerve terminals in a calcium dependent way and its extracellular concentration may be additionally elevated by the disease-related deficiency in ATP-hydrolyzing enzymes (Wieraszko and Seyfried 1989b). It is interesting to note that ATP release was not observed following low-frequency stimulation which evokes postsynaptic response but is unable to induce LTP. It appears that ATP is coreleased with a primary neurotransmitter (glutamate in this case) only with a certain pattern of stimulation. We suggested that ATP, while not involved in normal neurotransmission, may participate in the potentiation effect induced by high-frequency stimulation.

Further support for our suggestion came from experiments showing an influence of exogenous ATP on the size of the population spike. While 200 μM ATP depressed glutamate-evoked single neurones response (DiCori and Henry 1984) and attenuated the population spike (Dunwiddie and Hoffer 1980), lower concentrations of ATP (in nM range) induced potentiation of the synaptic response (Wieraszko and Seyfried 1989a, Nishimura et al. 1990, Wieraszko and Ehrlich 1994). As shown in Fig. 2A, 500 nM ATP gradually increased the size of the population spike. The increase in the population spike began shortly after ATP application and proceeded gradually to achieve a plateau within subsequent 20-30 min.

To elucidate further the role of the purinergic system in synaptic plasticity we evaluated the influence of different ATP analogs and P2 receptors antagonists on electrically induced LTP. Among the analogs tested only ATP-γ- S exerted an agonistic action, namely at low, micromolar concentrations ATP-γ- S by itself induced LTP (Fig. 2B). Although other analogs (e.g., AMPPNP) did not facilitate the potential, they prevented induction of a stable, non decremental LTP by HFS (Fig. 2C).

One of the possible explanations for the observed inhibition of LTP by ATP analogs can be the interaction of these analogs with P2-purinoreceptors. Based on the potencies of structural analogues of ATP, (Burnstock and Kennedy 1985), P2 receptors in non-neuronal tissues were classified into two subtypes: P2x and P2y. However, the pharmacological characterization of P2 receptors in the central nervous system is especially difficult, as competitive antagonists of P2 receptors, which simultaneously do not exhibit agonistic activity, have not yet been described (Fedan and Lamport 1990). None of the structural, nonhydrolyzable analogs tested (AMPPNP, α, β- methylATP, 2MeSATP), exerted any agonistic activity comparable with the action of ATP. In contrast, in other systems like the *vas deferens* and snail neurones (Yatani et al. 1982, Sneddon and Burnstock 1984) and cultured dorsal horn neurones (Jahr and Jessel 1983), one or more of these molecules were at least as potent as ATP. Therefore, it can be concluded that the amplification of the population spike by ATP observed in our study and confirmed by others (Nishimura et al. 1990, Fujii et al. 1995a) is not mediated by an interaction with one of the P2 receptors as classified to date. It should be pointed out, however, that the classification of ATP receptors is based mainly on the experiments performed on non-neuronal tissue (Wiklund et al. 1990) and therefore cannot provide complete explanation for all the effects observed by us and by others in CNS neurones (Illes and Nörenberg 1993). Different P2 receptors can probably coexist in multicellular preparation like the hippocampal slice and the final physiological effect may be a compound result of simultaneous activation of dif-

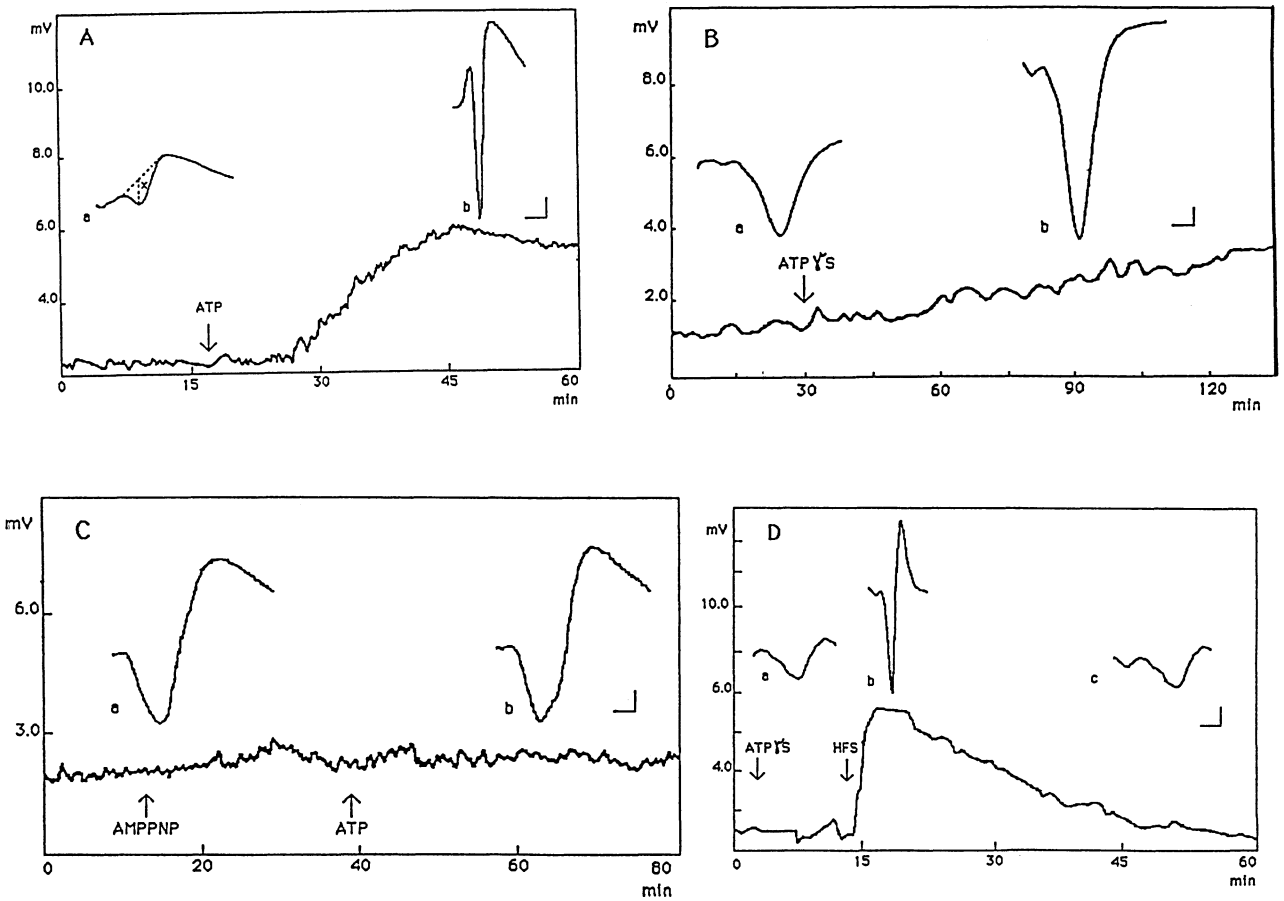

Fig. 2. The influence of ATP and ATP analogs on the hippocampal population spike. A, facilitation of the population spike by 500 nM ATP. Application of ATP is marked by an arrow. Traces a and b show the magnitude of the potential 10 min before and 30 min after application of ATP, respectively. In this and in the next figure upper trace depicts the shape of the potential, whereas the lower trace shows the changes in the size of the population spike with the time. The parameter X represents the size of the population spike as calculated by the computer. Calibration: 2 mS,0.6 mV; B, influence of ATP-γ- S (2.5 μM) on the magnitude of the population spike. An arrow indicated the time of ATP-γ- S application. Traces a and b demonstrate the magnitude of the population spike 5 min before and 70 min after ATP-γ- S application, respectively. Calibration: 2 mS, 0.7 mV; C, inhibition of facilitatory action of ATP by 9.7 μM AMPPNP. Application of AMPPNP and ATP is marked by arrows. Traces a and b represent the population spike 10 min before application of AMPPNP and 30 min after application of ATP, respectively. Calibration: 2 mS, 0.6 mV; D, ATP-γ- S (40 μM) applied before HFS prevents the induction of LTP (but note the presence of PTP). Traces a,b and c represent the shape of the population spike 15 min before and 2 and 30 min after application of HFS, respectively. Calibration: 2 mS, 0.7 mV. Reproduced from Wieraszko and Ehrlich (1994) with a kind permission of the publisher.

ferent subpopulations of P2 receptors. a, b- methylATP is a good example of variability observed in the reaction of P2 receptors to ATP analogs. It exerts an agonistic action in smooth muscles of the ear (Benham and Tsien 1987) and *vas deferens* (Friel 1988), and has a strong and weak antagonistic activity in cardiac muscle (Friel and Bean 1988) and hippocampal slices (Wieraszko and Ehrlich 1994), respectively. If the involvement of ATP analogs in the mechanism of LTP is mediated by interaction with receptors, their characteristics in the mammalian hippocampus must be different than P2 receptors described to-date in other tissues.

The facilitatory effect of both ATP (Fig. 2C) and ATP-γ-S (Wieraszko and Ehrlich 1994) was blocked by AMPPNP, a nonhydrolyzable analog of ATP that can act as agonist of P2 receptors (Moody and Burnstock 1993), and which by itself did not

exert any agonistic activity in our experiments. This indicates that hydrolysis of the gamma phosphate of ATP and ATP-γ-S is required for amplification of the population spike. As neither ATP nor ATP-γ-S can penetrate through the cell membrane, their hydrolysis must occur on the outer surface of the cell membrane with the participation of ectoATPases and/or ecto-protein kinases. ATP as a substrate of choice can be utilized by ATPases and protein kinases. ATP-γ-S can be readily utilized by protein kinase, but is poorly hydrolyzed by ATPases (Gratecos and Fischer 1974). The thiophosphorylation of proteins that occurs when a kinase uses ATP-γ- S proceeds at much slower rate then protein phosphorylation by ATP. This could explain the weaker and slower enhancement of the population spike by ATP-γ-S compared to ATP (compare Fig. 2A and B) and provides an additional argument for the necessity of hydrolysis of both molecules in order to be effective. As phosphoryl donors, ATP and ATP-γ-S enable protein phosphorylation on the cell surface, which in turn may regulate several synaptic processes (Ehrlich et al. 1988, 1990, Wieraszko and Ehrlich 1994, Fujii et al. 1995a, Chen et al. 1996). The finding that ATP-γ-S facilitates the potential at slower pace than ATP is consistent with the involvement of ecto-protein kinase. At 15 min following the application, ATP-γ-S, being slowly utilized by ecto-protein kinase, prevents induction of stable LTP instead of being a substrate. Prevention of LTP by 40 μM ATP-γ-S (only PTP was observed - Fig. 2D) resembles the action of ATP itself, which also did not exert agonistic activity at higher concentrations (Wieraszko and Seyfried 1989a, Wieraszko and Seyfried 1990). This again strengten the notion that ATP released by HFS does not participate in the induction of LTP, but rather in the maintenance as a substrate for ectokinase. Our recent experiments with monoclonal antibody termed M.Ab.1.9 which interacts with the catalytic domain of PKC (Mochly-Rosen and Koshland 1987, 1988) and selectively inhibits surface protein phosphorylation (Ehrlich et al. 1995, Chen et al. 1996) further support the idea of the involvement of ecto-protein kinase in LTP. While M.Ab.1.9 had no influence on the initial elevation of EPSP and population spike following HFS, it prevented establishing of permanent LTP (Ehrlich et al. 1995, Chen et al. 1996). The visualization of the interaction of M.Ab.1.9 with an externally oriented epitope on the surface membrane of unfixed brain synaptosomes has determined that ecto-PKC is concentrated in the region of junctional contacts, within the synaptic cleft (Lasher and Erickson 1995). This finding provides additional support for the idea of the involvement of ecto-protein kinase in the mechanism of LTP.

Independently of the question of whether the initial hydrolysis of ATP was carried out by an ATPase or protein kinase, an important consequence of extracellular ATP metabolism would be the generation of adenosine. Adenosine is generally considered an inhibitor of synaptic transmission (Salter et al. 1993), but it can also exert a strong facilitatory action on hippocampal neurones at low micromolar concentrations (Nishimura et al. 1990).

Additional support for the idea of extracellular site of ATP action came from the results obtained with suramin. This molecule which is unable to penetrate cellular membrane (Wilson and Wormall 1950, Fortes et al. 1973) is generally recognized as an antagonist of P2 receptors. Suramin facilitated hippocampal evoked potentials in a way which resembled the mechanisms involved in induction of LTP by HFS (Wieraszko 1995). The suramin amplified simultaneously the slope of EPSP, which is a measure of synaptic efficiency (Fig. 3A) and the amplitude of the population spike, which indicates the number of activated, pyramidal neurones (Fig. 3B). The suramin effect was blocked by AMPPNP, a weak agonist of P2 receptors (Fig. 3C). The AMPPNP effect was not due to a generalized action of the drug on synaptic transmissionor to a possible cytotoxic effect as a 10-fold increase in the strength of the stimulation triggered a much greater population spike (Fig. 3C, compare potential b and c). Additionally, suramin-induced potentiation occluded induction of LTP by HFS and was markedly reduced, although not abolished by NMDA receptor antagonists (Wieraszko 1995). Interestingly, suramin activates several kinases (Mahoney et al.

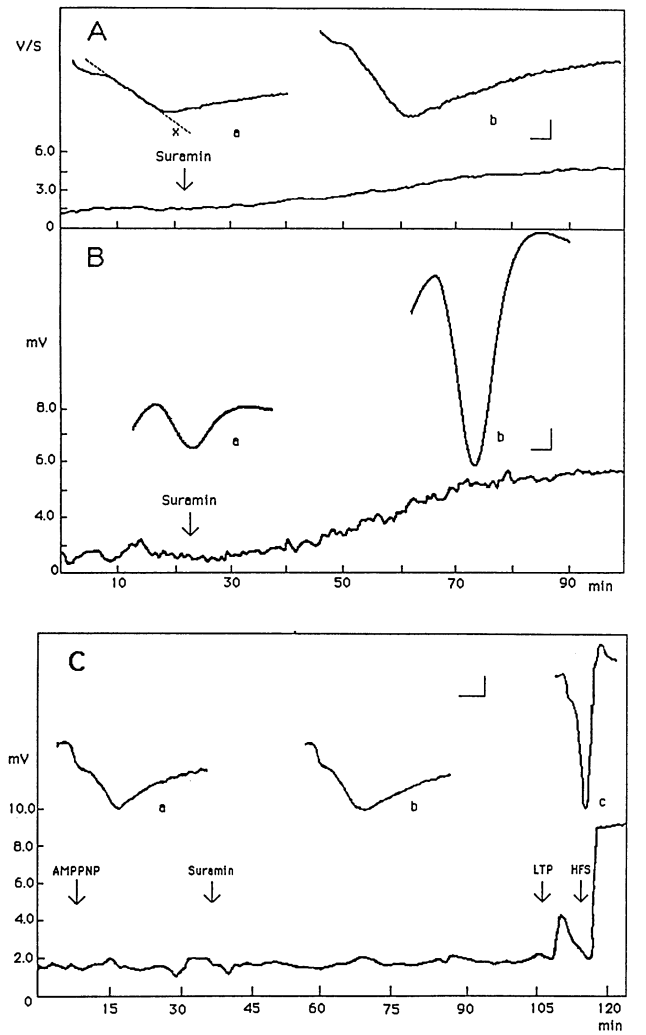

Fig. 3. The influence of suramin on hippocampal evoked potentials. A, the amplification of EPSP by 12 μM suramin. Parameter x marks the imaginary line drawn by the computer to calculate the slope of EPSP; B, the amplification of the population spike by 12 μM suramin. In both A and B, a and b represent the magnitude of the potentials before and after application of suramin, respectively. Calibration: 2 ms, 0.8mV (A); 2 ms, 0.5 mV (B); C, the inhibition of suramin effect by AMPPNP. Addition of AMPPNP (9.7 μM) and suramin (12 μM) is indicated by arrows. An unsuccessful attempt to induce LTP by electrical stimulation and a 10-fold increase in the strength of the stimulation are shown by LTP and HFS arrows, respectively; a and b indicate the magnitude of the population spike 10 min before and 45 min after suramin administration, respectively; c represents the population spike recorded immediately after the increase in the strength of the stimulation. Calibration: 2 ms, 0.7 mV. Reproduced from Wieraszko (1995) with a kind permission of the publisher.

1990) including ecto-protein kinase (Wixom and Sun 1995), which as already discussed, may modulate LTP through the process of surface protein phosphorylation.

It is also possible that the suramin effect is a result of interaction with P2 receptors. Although suramin is recognized as P2 receptor antagonist, it was unable to antagonize ATP action in oocytes (Kupitz and Atlas 1993). Interestingly, in these oocytes P2 receptors are also insensitive to the P2 receptor desensitizing agent, α,β-methylene-ATP, which was ineffective in blocking LTP in hippocampal slices as well (Wieraszko 1993, Wieraszko and Ehrlich 1994). Thus, it may be suggested that in the hippocampus suramin amplifies synaptic efficiency interacting with specific subpopulation of P2 receptors (activated by ATP or suramin) and/or by activating ecto-protein kinase. Therefore, we concluded that suramin amplified the synaptic efficiency in hippocampal slices in a way which involves mechanisms which also participate in induction and/or maintenance of LTP.

One has to consider a possibility that ATP analogs, used in our research could block the action of endogenous ATP by desensitization of ATP receptors (Bean et al. 1990). However, as not all of ATP analogs were equally potent in preventing of LTP, this type of action, exerted by ATP analogs seems to be very unlikely.

One of the essential steps in the induction of LTP is elevation of intracellular free Ca^{2+} concentration (Lynch et al. 1983). In other systems ATP is able to increase the intracellular Ca^{2+} level in several ways: activation of ATP-dependent Ca^{2+} channels (Yatani et al. 1982, Benham and Tsien 1987, El-Moatassin et al. 1992), activation of the phosphoinositol second messenger system (Lin and Chuang 1993) which triggers the release of Ca^{2+} from intracellular stores. These possible routes of elevation of Ca^{2+} could be inhibited by ATP analogs and result in prevention of LTP. Blockade of ATP receptors by ATP analogs could also diminish release of nitric oxide (NO). NO has been recently identified as endothelium-derived factor (EDRF) (Kelm et al. 1988) which is released by endothelial cells following stimulation

of purinergic receptors (Gordon 1990). Although research in the last few years demonstrated involvement of NO in several regulatory processes, including LTP (Bohme et al. 1991, Mizutani et al. 1993), the possibility that NO is released from neurones in the CNS following activation of purinergic receptors has not yet been investigated.

SUMMARY AND CONCLUSIONS

ATP is released from hippocampal slices following specific, high frequency stimulation of Schaffer collaterals nerve endings. This specific pattern of activation induces LTP which represents a permanent amplification of synaptic efficiency. The concentration of released, extracellular ATP depends on the time of stimulation and on the activity of ATP-hydrolyzing enzymes which have their active centre on the cell surface. ATP applied exogenously at low nanomolar concentrations can by itself permanently amplify synaptic efficiency. This action of ATP is blocked by ATP analogs and antagonists of purinergic receptors. The antagonistic action of ATP analogs and antagonists of purinergic receptors described here was directed mainly against the maintenance of LTP. Therefore, it appears that ATP does not play a role during routine neurotransmission in Schaffer collaterals, but exerts its effect only when high frequency stimulation induces permanent changes in the number of activated pyramidal neurones, which occurs following the induction phase of LTP. Thus, activation of a purinergic system is not essential for routine neurotransmission, but is involved in a particular event of synaptic activity, that leads to permanent changes in synaptic efficiency. When the action of ATP is blocked, permanent synaptic changes do not occur. Assuming that PTP represents the first phase of LTP (the induction), one can suggest that while induction of LTP remains unimpaired, the transition to the consolidation (maintenance) phase of LTP is prevented when the sites of ATP action are blocked. ATP analogs that can act as agonists of peripheral ATP receptors do not by themselves induce LTP, but are able to prevent LTP by interacting with sites of action of released ATP on the cell surface. These sites may include unique CNS purinergic receptors, and/or an active domain of the ectoenzymes responsible for ATP metabolism and for ATP utilization by extracellular protein phosphorylation systems. Further investigation is necessary to determine the exact biochemical mechanism underlying the involvement of extracellular ATP in the induction and maintenance of LTP.

ABBREVIATIONS

AMPPNP	adenylimidodiphosphate
ATP	adenosine 5'-triphosphate
ATP-γ-S	adenosine 5'-0-(thiotriphosphate)
α, β methyleneATP	α, β-methyleneadenosine 5'-triphosphate
EDRF	endothelium-derived factor
EPSP	excitatory postsynaptic potential
HFS	high-frequency stimulation
IP3	D-myo-inositol 1,4,5-triphosphate
LTP	long-term potentiation
M.Ab.1.9.	monoclonal antibody 1.9
2-MeSATP	2-methylthioadenosine
NMDA	N-methyl-D-aspartate
NO	nitric oxide
PKC	protein kinase C
PTP	postetanic potentiation

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